# Treatment with cinacalcet decreases systolic blood pressure in haemodialysed patients with chronic kidney disease and secondary hyperparathyroidism

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## Summary

**Background** There are numerous evidences suggesting that parathyroid hormone (PTH) plays a role in the pathogenesis of arterial hypertension. Treatment with cinacalcet decreases serum PTH concentration in haemodialysed patients with chronic kidney disease (HDP) and secondary hyperparathyroidism (sHPT) Chronic kidney disease is a pro-inflammatory state. The aim of this study was therefore to assess the influence of 6-month treatment with cinacalcet on blood pressure (BP) and inflammation markers in HDP with sHPT.

**Material and methods** In 58 HDP with sHPT serum PTH, interleukin-6, C-reactive protein, calcium and phosphate concentrations were assessed before the first dose of cinacalcet and after 3 and 6 months of treatment. BP was measured before haemodialysis sessions.

**Results** Serum PTH concentration decreased significantly after 3 and 6 months of cinacalcet treatment from 1138 (931–1345) to 772 (551–992); p<0.0001 and to 635 (430–839) pg/ml; p<0.0001, respectively. Systolic BP decreased after 3 and 6 months of treatment from 128 (123–133), to 125 (120–131) and to 121 (115–127) mm Hg, respectively (p for trend = 0.014). Diastolic BP did not change significantly. There were no significant differences in the number of antihypertensive drugs, vitamin D analogues dose and patients' body weight, nor the serum concentrations of IL-6 and CRP during the treatment period.

**Conclusions** 1. Six-month treatment with cinacalcet decreases systolic BP in haemodialysed patients with chronic kidney disease and secondary hyperparathyroidism. 2. The elucidation of exact pathomechanism of such a BP decrease needs further clinical studies, but it seems not to be related to inflammatory status changes.

**key words:** chronic kidney disease, secondary hyperparathyroidism, cinacalcet, blood pressure, haemodialysis

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## Background

Secondary hyperparathyroidism (sHPT) is among the most common abnormalities in haemodialysed patients with chronic kidney disease (CKD). The aetiopathogenesis of sHPT in CKD patients is complex and still not fully understood. Nevertheless, it can be generally summed up as the excessive parathormone (PTH) secretion caused by hyperphosphataemia, hypocalcaemia and low vitamin D status [1, 2].

PTH is regarded as one of the uraemic toxins and is one of the factors contributing to the pathogenesis of hypertension, which was documented in experi-

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mental studies [3], as well as in clinical studies conducted among others in maintenance haemodialysis (HD) patients [4, 5]. Moreover PTH seems to be associated with the increased cardiovascular burden in HD patients, in earlier stages of CKD as well as in general population [6–10].

Cinacalcet is a type II calcimimetic. Such compounds bind to the calcium receptor (CaR), which results in its increased sensitivity to serum calcium. This leads to the decrease of parathormone (PTH) production by the parathyroid glands [11, 12]. Cinacalcet is now commonly used in the treatment of secondary hyperparathyroidism in haemodialysed CKD patients. In the ACHIEVE study combined cinacalcet and small dose vitamin D treatment showed greater reduction in the progression of vascular and heart valve calcification compared to vitamin D alone [13–15].

Multiple lines of evidence suggest that PTH may be involved in the pathogenesis of hypertension. It has been shown that the excess serum PTH concentration in uraemia leads to the increase of calcium content in many cells and tissues (among them in blood vessels [16] and heart [17]). Results of animal experiments suggest that parathyroidectomy in 5/6 nephrectomised rats improved the endothelial dysfunction (normalized the synthesis of nitric oxide by the endothelial cells) [18]. Similar results were obtained from the clinical studies. Serum PTH concentration was found to be an independent predictor of the new-onset hypertension [19], as well as the left ventricle hypertrophy [20]. Moreover, parathyroidectomy causes the blood pressure decrease in patients with primary hyperparathyroidism [22].

It is well known that chronic kidney disease is a pro-inflammatory state. The results of recent studies have shown that the serum concentrations of markers of inflammation are significantly elevated in CKD patients [23–25]. Moreover, it was found that the extent of inflammation (measured by the neopterin concentration) is inversely related to the eGFR [26].

It has been shown that circulating PTH may stimulate the secretion of IL-6 in osteoblasts. This may be the cause of the elevated serum IL-6 concentration in secondary as well as in primary hyperparathyroidism. IL-6 is one of the main stimulants of the elevated synthesis of the so called acute phase proteins (e.g. CRP and fibrinogen) in the liver [27–29].

Taking into consideration the fact that PTH substantially contributes to the development of hypertension, it was reasonable to study the influence of 6-month cinacalcet treatment on blood pressure in haemodialysed patients with CKD and sHPT. Moreover, since PTH may induce IL-6 synthesis and cinacalcet reduces serum PTH concentration and taking into account the contribution of the inflammatory status in the pathogenesis of hypertension [32], it was interesting to assess the influence of cinacalcet on the blood pressure in in these patients.

## Materials and methods

Seventy-one adult, haemodialysed CKD patients (40 males, 31 females) with sHPT (defined as serum PTH concentration > 300 pg/ml) recruited from 9 different haemodialysis centres were enrolled in this clinical, prospective, open-label, single-arm study. Mean age of patients was 53.3 ± 14.8 years, median time of renal replacement therapy was 32 months [interquartile range (IQR) — 28 months]. Exclusion criteria were: age below 18 years, severe liver insufficiency, oversensitivity to any of the study drug compounds, high probability of non-compliance and suspected short life expectancy on renal replacement therapy.

Patients were treated with cinacalcet. Initial dose was 30 mg once daily and was modified, if needed, every 4 weeks depending on the serum PTH concentration. The target of treatment was to decrease serum PTH concentration to 150–300 pg/ml. Maximal dose of cinacalcet was 120 mg daily.

The doses of calcium carbonate and vitamin D analogues were flexible in order to avoid cinacalcet related hypocalcaemia and hypophosphataemia. Aluminium hydroxide was only used as a temporary "rescue" therapy in patients with severe hyperphosphataemia.

In every patient, plasma serum PTH (electrochemiluminescence; Roche, Mannheim, Germany), interleukin-6 (ELISA; R&D Systems, Abingdon, UK), C-reactive protein (ELISA; Immunodiagnostic AG, Bensheim, Germany), calcium and phosphate (Beckman Coulter UniCel DXC 600 analyser) concentrations were assessed before the first dose of cinacalcet and then after 3 and 6 months of treatment. Blood samples were collected before haemodialysis procedure in the middle of the week. After collection, blood samples were centrifuged, serum was aliquoted in 1ml test-tubes and then rapidly frozen in –70°C.

Moreover, in each patient arterial blood pressure was assessed on the brachial artery. The measurement was conducted before three consecutive haemodialysis sessions preceding the blood samples collection.

Statistical analyses were performed using the Statistica 10.0 PL software (StatSoft Polska, Cracow, Poland). Shapiro-Wilk test was used to test the variables distribution. Repeated measures ANOVA with

Bonferroni's correction for multiple comparisons, or alternatively Wilcoxon matched pairs test were used to assess the longitudinal changes of variables. Correlation coefficients were calculated using Spearman's rank correlation.

Results are shown as means with 95% confidence interval (CI), or as means with standard deviation, alternatively as median values with interquartile range (IQR) for variables with skewed distribution. Differences were considered significant when $p < 0.05$. The study protocol, adherent to Declaration of Helsinki, was approved by the Medical University of Silesia Bioethics Committee (KNW/0022/KB1/56/I/10 — 21.09.2010) and all patients gave their written informed consent for participation in the study.

## Results

From 71 enrolled patients, 58 (35 males, 23 females, mean age 53.8 ± 14.9 years) completed the study. Thirteen patients were ruled out of the study; among them 4 people died, 2 received kidney allograft, 2 patients discontinued the study because of permanent decrease of serum PTH concentration below 150 pg/ml, 2 underwent parathyroidectomy, one patient refused to continue the study due to paraesthesia; one patient withdrew the consent for the study and one moved out of the Silesian province.

The mean doses of cinacalcet after 3 and 6 months of treatment were 42 ± 17 mg and 51 ± 23 mg respectively. The doses of intestinal phosphate binders and active vitamin $D_3$ analogues were flexible in order to avoid hypocalcaemia and hypophosphataemia related to cinacalcet treatment. The percentage of patients treated with vitamin D analogues (alfacalcidol) and mean daily dose of alfacalcidol increased from 0.26 mg (0.17–0.36 mg) at the baseline, to 0.39 mg (0.25–0.52 mg); (p for trend = 0.04; Table 1). Moreover, there was a significant (p for trend = 0.01) decrease in the mean dose of aluminium hydroxide (Alusal) from 385 mg/day (170–410 mg/day) at the baseline, to 180 mg/day (15–350 mg/day) after 6 months of treatment. The number of patients treated with aluminium hydroxide also decreased (Table 1). The mean dose of calcium carbonate and the number of patients treated with this drug remained stable (Table 1).

In patients who completed the study cinacalcet treatment caused significant decrease of serum PTH from 1138 pg/ml (931–1345 pg/ml) at the baseline, to 772 pg/ml (551–992 pg/ml) after 3 month of treatment, and to 635 pg/ml (430–839 pg/ml) after 6 months of treatment (p for trend < 0.0001; Table 2). The mean decrease of serum PTH concentration after 3 and 6 months of treatment was 32.2% and 44.2%, respectively.

Six months of treatment with cinacalcet was associated with a significant (p for trend = 0.014) reduction of the mean systolic blood pressure from 128 mm Hg (122–133 mm Hg) at the baseline to 125 mm Hg (120–131 mm Hg) after 3 months and 123 mm Hg (118–128 mm Hg) after 6 months. There were no significant (p for trend = 0.14) differences in the diastolic blood pressure: 76 mm Hg (73–79 mm Hg), 76 mm Hg (73–79 mm Hg) and 75 mm Hg (71–77 mm Hg) — Figure 1.

In the entire study group there were no significant differences in the mean serum calcium and phosphate concentration during cinacalcet treatment

**Table 1.** Doses of alfacalcidol, intestinal phosphate binders and the number of patients using those drugs during cinacalcet treatment

| | Before treatment | After 3 months of treatment | After 6 months of treatment | *p* for trend |
|---|---|---|---|---|
| Dose of alfacalcidol [μg/24h] | 0.26 (0.17–0.36) | 0.32 (0.2–0.44) | 0.39* (0.25–0.52) | 0.04 |
| Number of patients treated with alfacalcidol | 30 (52%) | 34 (59%) | 40 (69%) | 0.06 |
| Dose of $CaCO_3$ [g/24h] | 3.49 (2.68–4.30) | 3.84 (2.95–4.72) | 3.88 (3.04–4.72) | 0.053 |
| Number of patients treated with $CaCO_3$ | 53 (91%) | 55 (95%) | 54 (93%) | 0.71 |
| Dose of aluminium hydroxide [mg/24h] | 385 (170–605) | 310 (80–540) | 180* (15–350) | 0.01 |
| Number of patients treated with aluminium hydroxide | 12 (21%) | 8 (14%) | 5 (9%) | 0.06 |

*p < 0.05 vs baseline (Bonferroni corrected)

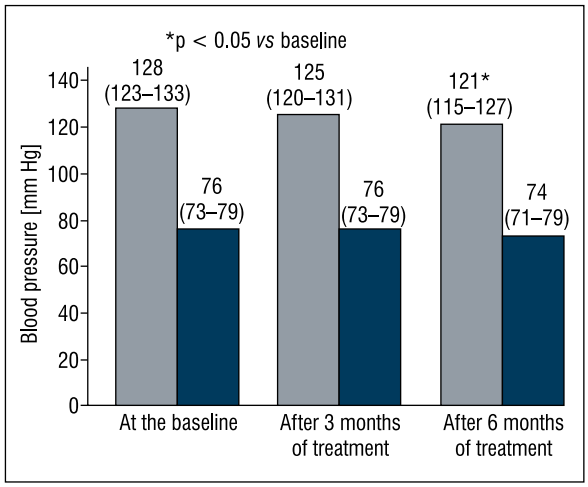


**Figure 1.** The changes of blood pressure during 6 months of cinacalcet treatment

nacalcet was observed. There were no significant differences in the patients' diastolic blood pressure.

Treatment with cinacalcet was not associated with any significant changes of the serum concentration of inflammation markers — the concentrations of both CRP and IL-6 remained stable during the observation period.

Secondary hyperparathyroidism is characterized by, among others, the excess of PTH secretion and PTH is one of the factors contributing to the development of hypertension in maintenance haemodialysis patients [33], patients in pre-dialysis stages of CKD [34], as well as in general population [35, 36]. Nevertheless there's only one paper published so far concerning the influence of cinacalcet on blood pressure in the maintenance haemodialysis patients. In the secondary analyses of the EVOLVE

**Table 2.** The changes of serum parathormone, inflammation markers, calcium and phosphate concentrations during the treatment with cinacalcet

| | Before treatment | After 3 months of treatment | After 6 months of treatment | *p* for trend |
|---|---|---|---|---|
| PTH [pg/ml] | 1138 (931–1345) | 772 (551–992) | 635 (430–839) | < 0.0001 |
| CRP [mg/l] | 11.2 (9.2–13.1) | 11.6 (9.4–13.7) | 10.5 (8.6–12.4) | 0.54 |
| IL-6 [pg/ml] | 5.76 (4.77–6.75) | 6.28 (5.11–7.45) | 5.72 (4.76–6.68) | 0.94 |
| Ca [mmol/l] | 2.15 (2.07–2.22) | 2.11 (2.04–2.17) | 2.09 (2.01–2.16) | 0.15 |
| Phosphate [mmol/l] | 2.02 (1.87–2.18) | 1.97 (1.80–2.14) | 1.89 (1.73–2.05) | 0.10 |

*p < 0.05 vs baseline (Bonferroni corrected)
PTH — parathormone; CRP — C-reactive protein; IL-6 — Interleukin 6; SBP — systolic blood pressure; DBP — diastolic blood pressure

(Table 2). Also, the mean serum concentrations of inflammation markers (CRP and IL-6) did not change significantly during the observation period.

There were no significant correlations between the changes of serum concentrations of PTH and markers of inflammation, nor the changes of the aforementioned and the changes of blood pressure. Moreover there were no significant correlations between the changes of PTH, inflammation markers or blood pressure and the dose of alfacalcidol.

## Discussion

In this multicentre prospective open-label single-arm clinical study a significant decrease of systolic blood pressure during the 6 months treatment with cinacalcet was observed. There were no significant differences in the patients' diastolic blood pressure.

Treatment with cinacalcet was not associated with any significant changes of the serum concentration of inflammation markers — the concentrations of both CRP and IL-6 remained stable during the observation period.

Secondary hyperparathyroidism is characterized by, among others, the excess of PTH secretion and PTH is one of the factors contributing to the development of hypertension in maintenance haemodialysis patients [33], patients in pre-dialysis stages of CKD [34], as well as in general population [35, 36]. Nevertheless there's only one paper published so far concerning the influence of cinacalcet on blood pressure in the maintenance haemodialysis patients. In the secondary analyses of the EVOLVE trial Chang *et al.* found that 20 weeks treatment with cinacalcet resulted in a 2.2 mm Hg decrease in systolic blood pressure and a 1.3 mm Hg decrease in diastolic blood pressure when compared with placebo. This is partly in agreement with the results of current study, as we found a 5 mm Hg decrease in the systolic blood pressure but no differences in the diastolic blood pressure after 6 months of treatment.

Similarly to the results of current and EVOLVE studies in patients after successful kidney transplantation the reduction of BP caused by the cinacalcet treatment was described [21].

In the study by Bonet *et al.* [37] the authors found no significant differences in central and peripheral blood pressure under a 12-month cinacalcet regimen, but they did describe a significant reduction of pulse wave velocity (PWV) and a decrease of

left ventricle mass (borderline significance p = 0.06). The reduction of arterial stiffness and the decrease of the development of cardiovascular calcifications caused by the treatment with cinacalcet may be one of potential explanations of our findings, while the lack of differences in the central and peripheral blood pressure in the study by Bonet *et al.* might be, at least to a point, explained by the low number of enrolled participants. Also they assessed blood pressure in the day between dialysis procedures and we did the measurements directly before the HD session what may also contribute to the differences in the BP values.

Interestingly, there were no significant differences in PWV in patients on peritoneal dialysis treated with cinacalcet [38]. Nevertheless, the number of enrolled subjects was also low in this study (only 19) and cinacalcet failed to lower the serum PTH concentration in substantial number of these patients.

Another potential explanation of our findings may be the fact that CaR is expressed in the cells of juxtaglomerular apparatus in the kidney [39]. Activation of CaR in these cells seems to decrease the plasma renin activity as it has been shown in both *in vitro* and *in vivo* studies [40, 31].

PTH stimulates the IL-6 synthesis and release. Elevated serum IL-6 contributes to the increase of CRP synthesis in the liver [27, 28]. We hypothesized that treatment with cinacalcet may thus lower both IL-6 and CRP concentration through the decrease of serum PTH concentration. Moreover, parathyroidectomy was shown to decrease serum concentration of inflammation markers in patients with primary hyperparathyroidism [41, 42]. It is well known that systemic inflammation participates in the pathogenesis of hypertension. However, in the current study no significant changes in either IL-6, or CRP concentrations were found after 6 months cinacalcet treatment. This is in agreement with the results published by Messa *et al.* In this study 6-month cinacalcet treatment didn't cause any changes in serum IL-6 concentrations [43]. Also the overall IL-6 concentrations were similar those obtained in our patients.

Our study has some unavoidable drawbacks. One is the lack of placebo treated control group. Another one is the fact that we did not have data from ABPM measurements, but only from the clinical measurements, which may cause bias because of the intradialytic volume changes in maintenance haemodialysis patients. We recognize our study as a hypothesis generating one and hope to encourage the conduction of other clinical studies, hopefully with the use of ABPM.

## Conclusions

In conclusion, we found that six-month treatment with cinacalcet decreases systolic BP in haemodialysed patients with chronic kidney disease and secondary hyperparathyroidism. The elucidation of exact pathomechanism of such a BP decrease needs further clinical studies, but it seems not to be related to inflammatory status changes.

## Conflict of Interests

None to declare.

## Funding

The study was the Department's statutory work.

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