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Original

Changes in Blood Pressure after the First Dose of Calcitonin (Elcatonin)

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Abstract: We had found previously that calcitonin treatment (elcatonin once a week for 10 weeks) results in significant decreases in blood pressure. The aim of the present study was to determine whether these effects were due to a cumulative effect of elcatonin or could be elicited by treatment with a single dose. To this end, we recruited 62 patients (eight men, 54 women; mean age 83 years; range 67–101 years) with a chief complaint of lower back pain to the present study and examined changes in blood pressure following administration of the first dose of elcatonin. All subjects in the study had been hospitalized either at our institution or an affiliated hospital. After acute phase symptoms had settled, subjects received 1 U (1 mL), i.m., elcatonin S20. Blood pressure was measured the day before the first scheduled treatment and on the day of treatment. Both systolic and diastolic blood pressure decreased from 2 h after administration, and dropped significantly 4 and 6 h after administration. Therefore, elcatonin decreased blood pressure without first having to be accumulated in the body. There are several possible explanations for the results, including effects mediated by changes in concentrations of calcitonin gene-related peptide and calcium ions, as well as involvement of the parasympathetic nervous system. In conclusion, calcitonin inhibits bone resorption and pain, lowers blood pressure, and is easy to use in elderly patients who exhibit age-related increases in blood pressure.

Key words: calcitonin, osteoporosis, blood pressure, elcatonin, blood flow

Introduction

Elcatonin is a calcitonin derivative that has an inhibitory effect on osteoporosis-related pain that is mediated via the serotonergic system[1, 2)]. In addition, it has been reported that elcatonin increases skin temperature[3)] and blood flow[4)], improves brachial-ankle pulse wave velocity, and decreases blood pressure[5, 6)]. Tissue blood flow improved significantly in individuals with decreased blood flow after the administration of elcatonin, and elcatonin has a significant hypotensive effect in patients with high compared with low blood pressure[6)] (Fig. 1). Generally, calcitonin is the only hormone that has been shown to lower serum calcium levels in vivo and to decrease high blood pressure and improve blood flow. In a previous study[6)], we found that

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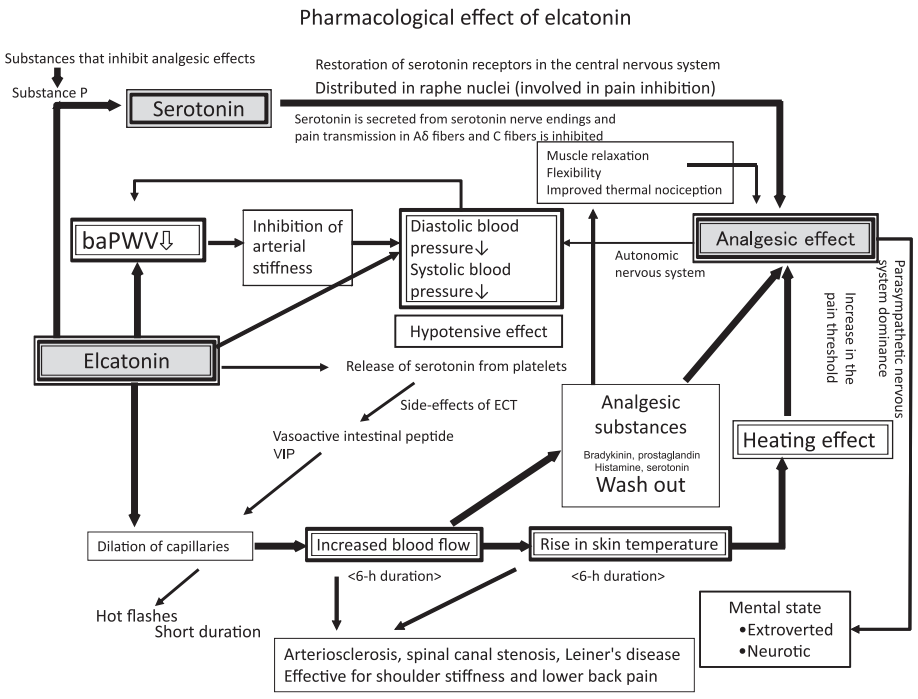

Fig. 1. Pharmacological effect of elcatonin (ECT). baPWV, brachial-ankle pulse wave velocity.

elcatonin treatment (once a week for 10 weeks) resulted in significant decreases in blood pressure compared with values in untreated patients. This hypotensive effect was thought to be due to the vasodilatory effect of calcitonin, although it was unclear whether it was due to a cumulative effect of 10 treatments or the result of a single dose of elcatonin. Therefore, the aim of the present study was to determine changes in blood pressure following the first administration of elcatonin.

Methods

Subjects

Sixty-two subjects (eight men, 54 women; mean age 83 years; range 67–101 years) with a chief complaint of lower back pain (thoracic compression fracture, lumbar spine compression fracture, lumbar spondylosis, spinal canal stenosis, spondylolisthesis, and muscular lower back pain) who had been admitted to our hospital or an affiliated hospital between 2009 and 2011 were recruited to the present study. Prior to their inclusion in the study, subjects were given an explanation of the study, including protection of personal information and ethical considerations, and were asked to provide oral or written consent.

Methods

After acute phase symptoms had settled and the subject was ambulatory and no longer required the use of a wheelchair, 1 U, i.m., elcatonin S20 (1 mL) was administered. Blood pressure was measured the day before the first scheduled treatment with elcatonin and on the day of treatment. Elcatonin was administered at 0900 hours and blood pressure was measured

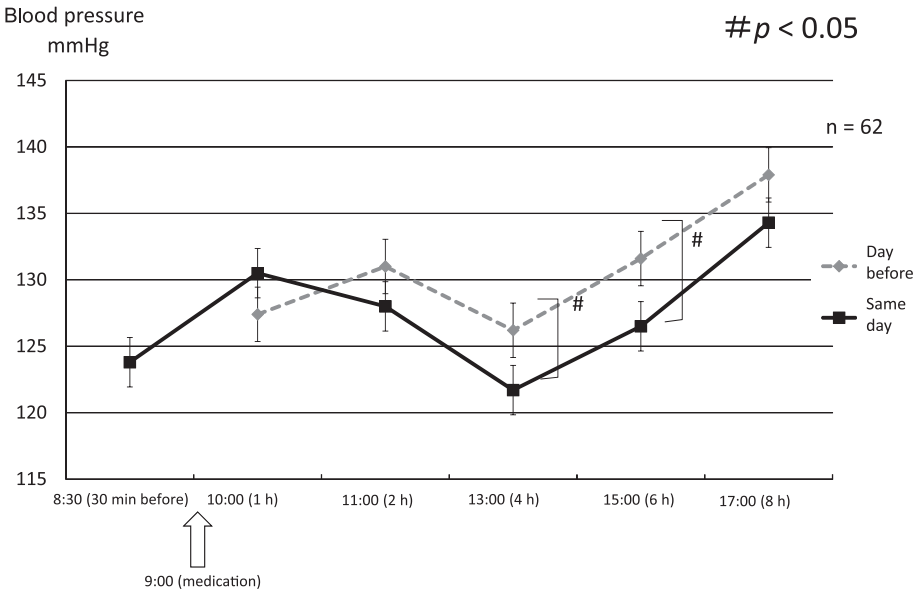

Fig. 2. Changes in systolic blood pressure the day before and on the same day of elcatonin administration. After injection of elcatonin, systolic blood pressure increased once, but was generally lower than on the day before, with significant decreases observed 4 and 6 h after administration. Data are the mean ± SD.

at the same time on both days (i.e. 1000, 1100, 1300, 1500, and 1700 hours) to minimize the effects of diet and rehabilitation on blood pressure fluctuations. Patients taking non-steroidal anti-inflammatory or antihypertensive drugs were maintained on these drug regimens at the same dosage and were given the drugs at the same time on both days. Blood pressure was measured using a manual sphygmomanometer after subjects had rested on a bed for 10 min.

Statistical analysis

Results are presented as the mean ± SD. For statistical analysis, blood pressure values taken at the same time on the day before and on the day of elcatonin treatment were compared using Student's t-test. Two-sided $P<0.05$ was considered significant. All analyses were performed using Stat Mate III ver. 3.14 (ATMS, Tokyo, Japan).

Results

Systolic blood pressure

Mean systolic blood pressure in all patients on the day before treatment at 1000, 1100, 1300, 1500, and 1700 hours was 127.4 ± 20.3, 131.0 ± 18.9, 126.3 ± 17.0, 131.6 ± 20.2, and 138.2 ± 22.5 mmHg, respectively. On the day of treatment, mean systolic blood pressure in all patients at 1000, 1100, 1300, 1500, and 1700 hours was 130.8 ± 20.6 ($P=0.19$), 128.0 ± 19.2 ($P=0.22$), 121.5 ± 18.2 ($P<0.05$), 126.5 ± 18.8 ($P<0.05$), and 134.9 ± 22.1mmHg ($P=0.22$), respectively, with significant decreases in systolic blood pressure 4 and 6 h after the administration of elcatonin compared with values obtained at the same time the previous day (Fig. 2).

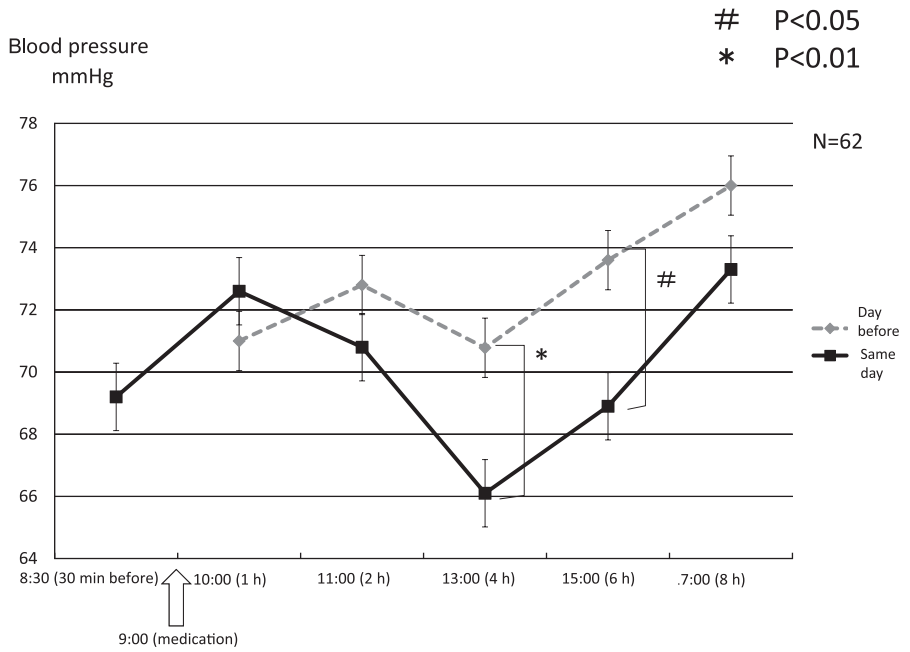

Fig. 3. Changes in diastolic blood pressure the day before and on the same day of elcatonin administration. After injection of elcatonin, diastolic blood pressure increased once, but was generally lower than on the day before, with significant decreases observed 4 and 6 h after administration. Data are the mean ± SD.

Diastolic blood pressure

Mean diastolic blood pressure in all patients on the day before treatment at 1000, 1100, 1300, 1500, and 1700 hours was 71.0 ± 11.5, 72.8 ± 13.6, 70.1 ± 13.1, 73.6 ± 12.4, and 76.2 ± 12.3 mmHg, respectively. On the day of treatment, mean diastolic blood pressure in all patients at 1000, 1100, 1300, 1500, and 1700 hours was 72.8 ± 14.9 ($P = 0.28$), 70.8 ± 14.0 ($P = 0.32$), 66.0 ±12.7 ($P < 0.01$), 68.9 ± 12.2 ($P < 0.05$), and 73.3 ± 12.2 ($P = 0.09$), respectively, with significant decreases seen 4 and 6 h after elcatonin treatment compared with values obtained at the same time the previous day (Fig. 3).

Discussion

Both systolic and diastolic blood pressure decreased ≥2 h after injection of elcatonin compared with values obtained the day before treatment, with a general trend for lower blood pressure after the administration of elcatonin compared with values obtained the previous day. Blood pressure levels were particularly low 4 and 6 h after elcatonin injection; therefore, elcatonin appears to decrease blood pressure without first having to accumulate in the body.

Elcatonin absorption following intramuscular injection is rapid, with peak plasma concentrations of approximately 30 pg / mL observed 30 min after administration of 20 U elcatonin[7]. However, pharmacokinetic analysis has revealed a half-life of 20.8 min for elcatonin and an absorption lag time of 5.5 min[8]. Based on these values, serum elcatonin concentrations were quite low 4 and

6 h after administration when the significant decreases in blood pressure were observed. There could be several factors contributing to the changes in blood pressure other than a direct action of calcitonin, including the actions of substances with a long half-life, such as calcitonin gene-related peptide (CGRP). The common calcitonin / CGRP gene on chromosome 11 is made up of six exons; calcitonin is encoded by exon 4 and CGRP is encoded by exons 5 and 6[9]. Calcitonin is produced by thyroid C cells through tissue-specific splicing, whereas CGRP is produced by neurons that are widely distributed throughout the cardiovascular system, but are more common in the arterial than venous system[10]. CGRP and calcitonin reportedly share 20% homology[11], and calcitonin has a vasodilatory effect via CGRP-like activity. Another factor that could have contributed to the changes in blood pressure seen in the present study is lowering of calcium ion levels. Because the production of calcitonin results in decreases in extracellular calcium levels, there is a consequent decrease in calcium influx into cells via calcium-sodium transporters[12], resulting in a decrease in the opening of calcium-dependent calcium channels in the sarcoplasmic reticulum[13]. This weakens the contractile force of the cardiovascular system and subsequently decreases blood pressure. In addition, changes in blood pressure following the injection of elcatonin may involve effects of the parasympathetic nervous system. Calcitonin administration induces descending pain inhibition via the serotonergic system; following pain alleviation, the parasympathetic nervous system becomes dominant, resulting in vasodilation[1]. This mechanism is considered to be important based on studies reporting significant therapeutic effects of elcatonin administered for the treatment of reflex sympathetic dystrophy[14]. Furthermore, calcitonin administration restores serotonin receptor levels, decreases the release of glutamic acid, and eliminates hypersensitivity, thereby improving osteoporosis pain[1]. However, serotonin receptor levels are restored following repeated dosing with elcatonin, and not after treatment with a single dose, thus it remains unclear whether the effects of the parasympathetic nervous system on blood pressure are predominant after the administration of a single dose of elcatonin.

In Japan, the drugs used in the treatment of osteoporosis have changed considerably in recent years. For example, bisphosphonates, including alendronate and risedronate, are commercially available and are taken once a week; oral minodronate and intravenous alendronate are taken once a month. In 2010, the selective estrogen-receptor modulators raloxifene and bazedoxifene, as well as drugs inhibiting bone resorption, such as vitamin D_3 and eldecalcitol, were introduced in addition to calcium and vitamin K_2 treatment[15]. Parathyroid hormone effectively promotes osteogenesis, whereas calcitonin inhibits bone resorption[16] and acts to inhibit pain. Furthermore, drugs that also have hypotensive effects are considered safe and easy to use in elderly patients with age-induced increases in blood pressure. Therefore, tailored treatment for individual patients using suitable drug combinations is recommended in these cases.

Systolic and diastolic blood pressure levels were decreased significantly between 4 and 6 h after administration of the calcitonin analog elcatonin, which was found to be effective, safe, and easy to use in elderly patients with osteoporosis.

Conflict of interest

The authors have declared no conflict of interest.

References

1) Ito A, Kumamoto E, Takeda M, *et al*. Mechanisms for ovariectomy-induced hyperalgesia and its relief by calcitonin: participation of 5-HT1A-like receptor on C-afferent terminals in substantia gelatinosa of the rat spinal cord. *J Neurosci*. 2000;**20**:6302–6308.
2) Nagai T, Sakamoto K, Munechika K, *et al*. Psychological effect of osteoporosis drug formulation on osteoporosis patients. *Osteoporos Jpn*. 2012;**20**:74–79.
3) Nagai T, Sakamoto K, Miyaoka H. The skin temperature-increasing activity of calcitonin (elcatonin). *J Jpn Soc Bone Morphom*. 2005;**15**:15–20. (in Japanese).
4) Nagai T. The effect of calcitonin (elcatonin) on blood flow. *J Showa Med Assoc*. 2007;**67**:469–478. (in Japanese).
5) Nagai T, Sakamoto K, Miyaoka H, *et al*. Effect of elcatonin on brachial-ankle pulse wave velocity: a preliminary report. *J East Jpn Assoc Orthop Traumatol*. 2009;**21**:545–549.
6) Nagai T, Sakamoto K, Inagaki K, *et al*. Effects of calcitonin preparation (elcatonin) on blood pressure and pulse wave velocity. *J East Jpn Assoc Orthop Traumatol*. 2010;**22**:33–41.
7) Takeyama M, Ikawa K, Eto I, *et al*. Enzyme immunoassay of elcatonin in human plasma. *Biol Pharm Bull*. 1995;**18**:900–902.
8) Takeyama M, Ikawa K, Nagano T, *et al*. Elcatonin raises levels of vasoactive intestinal peptide in human plasma. *J Pharm Pharmacol*. 1996;**48**:657–659.
9) Rosenfeld MG, Mermod JJ, Amara SG, *et al*. Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. *Nature*. 1983;**304**:129–135.
10) Holzer P. Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience*. 1988;**24**:739–768.
11) Born W, Beglinger C, Fischer JA. Diagnostic relevance of the amino-terminal cleavage peptide of procalcitonin (PAS-57), calcitonin and calcitonin gene-related peptide in medullary thyroid carcinoma patients. *Regul Pept*. 1991;**32**:311–319.
12) Freichel M, Zink-Lorenz A, Holloschi A, *et al*. Expression of a calcium-sensing receptor in a human medullary thyroid carcinoma cell line and its contribution to calcitonin secretion. *Endocrinology*. 1996;**137**:3842–3848.
13) Striggow F, Ehrlich BE. Ligand-gated calcium channels inside and out. *Curr Opin Cell Biol*. 1996;**8**:490–495.
14) Ide J, Yamaga M, Kitamura T, *et al*. Quantitative evaluation of sympathetic nervous system dysfunction in patients with reflex sympathetic dystrophy. *J Hand Surg Br*. 1997;**22**:102–106.
15) Matsumoto T, Miki T, Hagino H, *et al*. A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. *J Clin Endocrinol Metab*. 2005;**90**:5031–5036.
16) Ikegame M, Ejiri S, Ozawa H. Histochemical and autoradiographic studies on elcatonin internalization and intracellular movement in osteoclasts. *J Bone Miner Res*. 1994;**9**:25–37.

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