# The influence of norethisterone acetate on urinary urodilatin excretion in postmenopausal women

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**Summary**

We have previously found that transdermal estradiol application significantly stimulated the urinary excretion of urodilatin, a newly discovered renal peptide with diuretic properties. It is well established that the addition of progestogen is necessary in hormone replacement therapy in women with an intact uterus. This study was designed specifically to examine the effect of progestogen norethisterone acetate (NETA) in postmenopausal women. NETA given alone orally in dosages of 1 mg/d and 2 mg/d for 10 days, as used for the progestogen-challenge test, did not increase urodilatin excretion. NETA in combination with estradiol, administered orally and transdermally in the second half of a 4-week estradiol treatment cycle, did not significantly change urodilatin excretion. The results of the present study indicate that NETA addition to estrogen replacement therapy may antagonize the stimulating estradiol effect on urodilatin production as registered in our earlier study.

*Key words:* Norethisterone acetate; Postmenopausal women; Urinary urodilatin excretion.

## Introduction

The natriuretic peptides consist, as far as has been identified to date, of four members, i.e. the A- (ANP), B- (BNP), C-type (CNP), and urodilatin. ANP and BNP are mainly synthesized in the heart whereas CNP is mainly found in the brain [1, 2, 3]. Urodilatin is thought to be exclusively synthesized in the kidney [4]. All four peptides are similar in their chemical structure and are characterized by a ring motif of 17 amino acids bridged by a disulfide bond between two cysteine residues. Urodilatin seems to elicit the greatest effect on renal sodium and water excretion [4].

Data on the significance of sex steroids and renal function are scarce but there are some indications that estrogens may have a nephroprotective effect [5]. As yet little is known about the influence of sex hormones on the synthesis of urodilatin. In a previous study we examined the effect of estradiol replacement therapy in postmenopausal women [6]. Transdermal estradiol significantly increased urodilatin synthesis after 4 weeks' treatment. The present study was designed to investigate the effect of the progestogen norethisterone acetate (NETA) used in the hormone replacement therapy (HRT) of postmenopausal women. The addition of progestogen to estradiol replacement therapy is mandatory in women with an intact uterus to avoid the development of endometrial cancer.

## Patients and methods

Thirty-seven postmenopausal women with climacteric complaints were enrolled in the study. All women had stopped menstruating at least 12 months previously. Pre-treatment 17ß-estradiol levels in serum were below 70 pmol/l and FSH levels were above 40 IU/l. In this open study 20 women (group A) were treated with norethisterone acetate (NETA) 2 mg/d orally for 10 days as a progestogen-challenge-test. After a wash-out phase of 8 days the patients were treated for 9 days with estradiol valerate (E2) 2 mg/d orally and consecutively 12 days with an oral combination of E2 (2 mg/d) and NETA (1 mg/d). Seventeen women (group B) were treated with NETA 1 mg/d orally for 10 days as a progestogen-challenge-test and after a wash-out phase of 8 days the patients received estradiol (0.05 mg/d) transdermally for 14 days and a combination of estradiol (0.05 mg/d) with NETA (0.25 mg/d) transdermally for 14 days. Patients with a history of kidney disease were excluded from the study. Pre-treatment examinations did not show any signs of impaired kidney function; the urinary creatinine values did not change throughout the study.

Morning urine accumulated during the night between 10 pm and 6 am was collected before and after hormonal treatment. The morning collection of night urine provided a convenient and reliable way of sampling and a concise comparable time period well-defined by the resting condition during sleep. Aliquots of the urine were frozen at -20° C until assayed.

Urodilatin levels were determined by radioimmunoassay (Immunodiagnostik GmbH, Bensheim, Germany). Inter- and intraassay variation coefficients were 10.6% and 9.2%, respectively.

Absolute values, expressed in ng urodilatin/8h urine excretion, were compared by ANOVA and relative values, expressed as a percentage of the pre-treatment value, were compared by the Student's t-test.

## Results

The basic clinical data of the patients in both study groups are given in Table 1. No significant differences were observed between the two groups.

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Table 1. — *Basic clinical data of the treated patients (means ± SD)*

| | Group A 20 patients | Group B 17 patients |
|---|---|---|
| Age (years) | 54.8±4.4 | 53.5±6.0 |
| Height (cm) | 163.3±6.7 | 164.1±6.2 |
| Weight (kg) | 73.6±11.8 | 67.3±7.8 |
| Time since menopause (years) | 4.8±3.6 | 6.7±7.5 |

Table 2. — *Absolute urinary excretion values of urodilatin (ng/8h) and relative values as percentages of the pre-treatment values = 100% in postmenopausal women after hormonal replacement therapy (means ± SEM)*

| | | |
|---|---|---|
| *Absolute urodilatin excretion values* | | |
| NETA | pre-treatment | 10 days' treatment |
| 1 mg/d | 35.6 (8.8) | 41.5 (9.6) |
| 2 mg/d | 25.5 (2.8) | 33.5 (2.9) |
| Estradiol/NETA | pre-treatment | 1 cycle treatment |
| oral | 35.6 (8.8) | 33.1 (5.5) |
| transdermal | 25.5 (2.8) | 33.8 (3.4) |
| *Relative urodilatin excretion values* | | |
| NETA | pre-treatment | 10 days' treatment |
| 1 mg/d | 100% | +51.8 (24.9) |
| 2 mg/d | 100% | +55.9 (23.2) |
| Estradiol/NETA | pre-treatment | 1 cycle treatment |
| oral | 100% | +47.4 (31.7) |
| transdermal | 100% | +64.8(90.5) |

The absolute values of urodilatin excretion are summarized in Table 2. The pre-treatment values were 35.6 ng/8h (SEM 8.8) in group A and 25.5 ng/8h (SEM 2.8) in group B. After NETA treatment for 10 days with 1 mg/d and 2 mg/d the urodilatin values were 41.5 ng/8h (SEM 9.6) and 33.5 ng/8h (SEM 2.9), respectively. No statistically significant differences from the pre-treatment values were observed for either NETA dosages. After estradiol combined other NETA treatment the results after 1 cycle of treatment were 33.1 ng/8H (SEM 5.5) in the oral group; 33.8 ng/8h (SEM 3.4) in the transdermal group. No statistically significant changes in the absolute urodilatin values were found for either route of hormonal replacement therapy.

As there was wide individual variation in the pre-treatment values, it is more meaningful to express the changes produced by the hormone treatment as a percentage of the individual pre-treatment values. Because each patient's data is transformed in this way, inter-individual differences in metabolism are taken into account.

In Table 2 the relative changes of urodilatin excretion compared to the pre-treatment values are depicted. With NETA treatment alone the values for the 1 mg/d dose were +51.8% (SEM 24.9) and for the 2 mg/d dose +55.9% (SEM 23.2), however there was no significant difference.

After 1 cycle of treatment with oral estradiol/NETA combination, the urodilatin values increased by 47.4% (SEM 31.7), and after 1 cycle transdermal administration of the estradiol/NETA combination by 64.8% (SEM 90.5). The increases were in both cases in comparison to the pre-treatment value not found to be statistically significant.

## Disscussion

Estradiol replacement therapy in postmenopausal women is widely used for alleviating menopausal syndrome and preventing osteoporosis and cardiovascular disease [7]. In addition it can be assumed that estrogens may also be nephroprotective [5]. This is of clinical significane because it is well known that kidney function decreases with aging. In a previous study comparing oral with transdermal estradiol treatment, transdermal therapy showed a significant increase of urodilatin excretion after 4 weeks' treatment whereas oral replacement therapy only showed a tendency to increase [6]. As urodilatin regulates electrolyte and water reabsorption and reduces blood pressure [4], an enhancing effect on its synthesis by estradiol may contribute to the vasodilation caused by estrogens.

The addition of a progestogen in non-hysterectomized women to prevent endometrial hyperplasia is often associated with an antagonism of estrogen actions. Norethisterone acetate (NETA), a C19-progestogen with partially androgenic properties, is a commonly used progestogen in HRT which has been shown to have an impact on beneficial estradiol effects on the lipid profile [8]. We have shown that NETA reduces an estradiol-induced serotonin increase in postmenopausal women [9]. Thus NETA may antagonize, at least in part, estradiol-mediated beneficial effects on the cardiovascular system.

The results presented show that NETA alone had no effect on urinary urodilatin excretion although a tendency to an increase could be observed. Since NETA is vasoconstrictive [8] this effect could be interpreted as a counterbalancing hemodynamic reaction. In contrast the addition of NETA to estradiol seems to abolish the positive effect of estradiol on urodilatin synthesis. No significant increase in urodilatin production was registered after the combined estradiol/NETA treatment in contrast with what was seen in our previous study with estradiol treatment alone.

The impact of the addition of progestogen may, however, depend on structure, dosage, duration, and administration mode of the progestogen. Long-term studies, therefore, are necessary to further elucidate whether NETA and other progestogens in use for HRT are antagonizing the stimulating effect of estradiol on urodilatin synthesis.

## References

[1] Forssmann W. G.: "Cardiac hormones. I. Reviews on the morphology, biochemistry, and molecular biology of the endocrine heart". *Eur. J. Clin. Invest.*, 1986, *16*, 439.

[2] Sudoh T., Minamino N., Kangawa K., Matsuo H.: "A new natriuretic peptide in porcine brain". *Nature*, 1988, *332*, 78.

[3] Schulz-Knappe P., Forssmann K., Herbst F., Hock D., Pipkorn R., Forssmann W. G.: "Isolation and structural analysis of 'urodilatin', a new peptide of the cardiodilatin-(ANP)-family, extracted from human urine". *Klin. Wochenschr.*, 1988, *66*, 752.
[4] Meyer M.: "Urodilatin - Von Entdeckung zu klinischer Anwendung". I. Holzapfel Verlag München, 1997.
[5] Ritz E.: "Sind Niereerkrankungen geschlechtsspezifisch"? *Ärzte-Zeitung*, 1998, *48*, 10.
[6] Seeger H., Armbruster F. P., Mueck A. O., Lippert T. H.: "The effect of estradiol on urinary urodilatin excretion in postmenopausal women". *Arch. Gynecol.*, in press.
[7] Lobo R. A.: "Treatment of postmenopausal woman: Basic and clinical aspects". First edition. New York. Raven Press Ltd., 1994.
[8] Kuhl H.: "Metabolische Effekte der Östrogene und Gestagene". Gynäkologe 1997, *30*, 357.
[9] Mueck A. O., Seeger H., Kaßpohl-Butz S., Teichmann A. T., Lippert T. H.: "Influence of norethisterone acetate and estradiol on serotonin metabolism of postmenopausal women". *Horm. Metab. Res.*, 1997, *29*, 80.

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