Ophthalmic Artery Vasodilation after Intranasal Estradiol Use in Postmenopausal Women

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Aim: The study aim was to evaluate the acute hemodynamic effects of intranasal 17-beta-estradiol on ophthalmic arterial circulation in postmenopausal women.

Methods: Twenty-one healthy women in natural menopause for at least 6 months (mean age: 53.2 ± 2.9 years) were investigated. Each patient received 300 μg intranasal 17-beta-estradiol. We evaluated the heart rate, systolic and diastolic blood pressure, ophthalmic artery velocity at systolic and diastolic peak and its flow curve integral (FCI) before and 30, 60 and 180 minutes after the administration of the drug.

Results: At all time points, the ophthalmic artery FCI showed statistically significant variations (p < 0.001) of velocity (cm/sec) compared to T0 (speed recorded at baseline before drug administration). Moreover, systolic blood pressure, diastolic blood pressure and heart rate did not significantly differ each other after drug administration.

Conclusions: Administration of a single dose of intranasal 17-beta-estradiol to healthy postmenopausal women increases ophthalmic artery perfusion.


Key words: Estrogen therapy, Ophthalmic artery, Cerebral circulation, Menopause, Estradiol

Introduction

Estrogens exert a vasodilatory effect on peripheral arteries by direct action on endothelium functions1-3). The vasomotor effect depends upon genomic action on b-estrogen receptors, which activates nitric oxide (NO) synthase and consequently increases NO production, thus modulating vasoreactivity. Both acetylcholine-induced and flow-dependent vasodilation are preserved or potentiated by estrogen treatment in both animal models and humans. Moreover, by increasing the endothelial production of NO and prostacyclin, estradiol (E2) may prevent the early formation of atheromasic lesions4). However, estrogens show vasodilatory effects only in arteries with a normal endothelium and the effects may be attenuated or even abolished in arteries with endothelial dysfunction5). Relevantly, similar effects of estrogens have been demonstrated also on human coronary vessels6). The nasal route is an effective and well-established route for E2 delivery6). Nasal administration produces a pulsed profile of plasma E2, with systemic plasma levels rising rapidly and returning to pre-administration levels within 12 h7). Transmucosal administration of drugs may lead to preferential distribution to nearby organs by different mechanisms. Accordingly, we have demonstrated
that, after transvaginal administration, steroids may distribute preferentially to the uterus thanks to the existence of local distribution mechanisms mostly based on counter-current transfer from veins to arteries. After vaginal administration of progesterone, the endometrial levels of the hormone were markedly higher than those expected based on the reached systemic levels. Similarly, vaginal administration of micronized E2 results in preferential absorption of E2 into the endometrium, consistent with a “uterine first pass” effect.

The occurrence of the preferential distribution of drugs from the nasal mucosa to the brain has been demonstrated throughout areas in which the blood-brain barrier does not work (BBB). Anatomically, the carotid artery passes through the cavernous sinus, which collects blood draining into the nasal cavity, and therefore it is possible to speculate that the counter-current passage of drugs from the venous blood to the carotid artery may take place.

**Aims**

The aim of this study was to evaluate whether, after intranasal administration of E2, local preferential distribution of the hormone to the head and eyes takes place. For this purpose, the acute hemodynamic effects of intranasal E2 administration on eye blood supply (ophthalmic artery) and the systemic artery (tibial artery) were compared in postmenopausal women. The hemodynamic evaluation was based on the comparison of arterial FCI (flow curve integral) after well-established intervals among infusions.

**Methods**

Twenty-one healthy volunteers women, in menopause for 3.6 ± 1.9 years, aged 53.2 ± 2.9 years (mean ± SD), attending the Section of Cardiovascular Diseases, Department of the Emergency and Organ Transplantation of Bari University General Hospital (Italy), were enrolled in the study. The average weight of patients was 67 ± 7.3 kg. General characteristics of the study population are shown in Table 1, according to the findings of our research. Menopause condition was established basing on amenorrhea for 12 months and laboratory findings of serum levels E2 < 30 pg/mL and FSH > 40 mIU/mL. None of the women recruited were taking hormone replacement therapy for menopause or drugs or substances acting on the cardiovascular system or were in a position to determine vasomotor alterations.

Exclusion criteria were: obesity defined as body mass index [BMI calculated as weight (in kilograms)/height (in meters)^2] > 30, hypertension (defined as systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg, or a pharmaceutical history of antihypertensive drug use), history of headache, history or presence of thrombotic disease or hormone-sensitive cancers, severe alterations in glucose, lipid and liver enzyme serum concentrations, severe nasal obstruction and allergic rhinitis.

The patients were informed about the aim of the study and gave written consent. The study was approved by the Institutional Review Board of Bari University General Hospital and was carried out in accordance with the principles of the Helsinki Declaration.

All patients received a single dose per nostril of a nasal spray formulation containing E2 and cyclodextrin as the carrier (Sprediol; Stroder, Florence, Italy) corresponding to a dose of 300 μg E2. All intranasal applications were performed by the same health care professional.

**Table 1.** General characteristics of study population. Heart rate, systolic and diastolic pressure were measured at baseline (T0) and after 30 (T30), 60 (T60) and 180 (T180) minutes.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Patients (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.2 ± 2.9</td>
</tr>
<tr>
<td>Years of menopause (n)</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 7.3</td>
</tr>
<tr>
<td>Heart rate (beats per minute, bpm)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>79 ± 9.8</td>
</tr>
<tr>
<td>T30</td>
<td>69.6 ± 6.6</td>
</tr>
<tr>
<td>T60</td>
<td>71.5 ± 7.8</td>
</tr>
<tr>
<td>T180</td>
<td>73.1 ± 7.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>121.7 ± 9.2</td>
</tr>
<tr>
<td>T30</td>
<td>123.7 ± 8.4</td>
</tr>
<tr>
<td>T60</td>
<td>123.2 ± 8.7</td>
</tr>
<tr>
<td>T180</td>
<td>122 ± 8.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>76 ± 7.5</td>
</tr>
<tr>
<td>T30</td>
<td>77.7 ± 5.7</td>
</tr>
<tr>
<td>T60</td>
<td>78.5 ± 5.9</td>
</tr>
<tr>
<td>T180</td>
<td>75.2 ± 7.3</td>
</tr>
<tr>
<td>E2 plasma concentrations (pg/mL)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>11.5 ± 5.3</td>
</tr>
<tr>
<td>T30</td>
<td>499.3 ± 223.3</td>
</tr>
<tr>
<td>T60</td>
<td>243.7 ± 112.4</td>
</tr>
<tr>
<td>T180</td>
<td>91.1 ± 39.6</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD. p < 0.05 was significant.
Before and 30, 60 and 180 minutes after administration, the patients were evaluated as regards the following hemodynamic parameters: heart rate, systolic and diastolic blood pressure, Doppler flowmetry of the ophthalmic and posterior tibial arteries with evaluation of flow rates at systolic and diastolic peaks and computation of the flow curve integral (FCI).

Doppler flowmetry was performed in spectral analysis mode with an HP Agilent Sonos 1000, using a probe of 5 MHz CW as follows:

For the ophthalmic artery, recording was at level of the medial angle of the eyes (within the vessel exiting the homonymous foramen) with an angle incidence near 0°. In particular, the subject was positioned supine, with the head lifted about 25-30°. We tried to exert as little pressure as possible on the eye in order to avoid alterations in our calculations. The ophthalmic artery could be detected medially to the optic nerve, near the nasal region of the ocular globe. Approximately 10-15 mm behind the globe has been established as the zone where the ophthalmic artery could be identified. The position of the sample volume was adjusted in order to reduce the angle correction and obtain the best possible result of our analysis;

For the posterior tibial artery, recording was performed at the level of the medial malleolus with an angle incidence <20°.

Statistical Analyses

The data are expressed as the mean ± SD. For statistical evaluation, analysis of variance (ANOVA) was used. *P* < 0.05 was considered significant.

Results

The measurements were performed successfully in all patients and no side-effects were recorded. No significant variation was observed in the heart rate, systolic and diastolic pressure at any time after administration. Table 1 shows the mean values of plasma E2 concentrations at baseline and 30, 60 and 180 minutes after E2 administration.

In contrast, the nasal administration of E2 was followed by significant variations in the ophthalmic artery but not in the tibial artery circulation. Hemodynamic parameters and values of FCI calculated in the two arterial districts investigated at different times are displayed in Table 2.

After E2 administration, the FCI in the ophthalmic artery showed a rapid and sustained increase so that values at 30, 60 and 180 min were significantly higher than at baseline (*P* < 0.001). In contrast, no significant variation was observed in the tibial artery.

Table 2. Values of the flow curve integral (FCI) in the ophthalmic and tibial artery before (0) and 30, 60 and 180 min after E2 nasal administration. Values are expressed as the mean ± SD

<table>
<thead>
<tr>
<th>Minutes</th>
<th>FCI ophthalmic artery</th>
<th>FCI tibial artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.12 ± 2.1</td>
<td>2.85 ± 1.06</td>
</tr>
<tr>
<td>30</td>
<td>10.9 ± 2.36*</td>
<td>3.09 ± 1.09</td>
</tr>
<tr>
<td>60</td>
<td>10.47 ± 1.5*</td>
<td>2.95 ± 1.07</td>
</tr>
<tr>
<td>180</td>
<td>10.71 ± 2.17*</td>
<td>2.62 ± 0.74</td>
</tr>
</tbody>
</table>

* *P* < 0.001

FCI. In detail, the FCI in the ophthalmic artery showed a percentage increase of 40.21, 35.48 and 38.12% at 30, 60 and 180 min, respectively, whereas FCI variations in the tibial artery varied from +11.9% to −5.47% (Fig. 1).

Discussion

The data from this study demonstrate that, after intranasal E2 administration, there is a rapid and sustained vasodilatory effect in the ophthalmic artery but not in peripheral arteries. In detail, 30 minutes after administration, ophthalmic artery flow was increased by about 40.21%. A similar vasodilatory effect was maintained up to 180 min. In contrast, in the tibial artery no significant variation in flow circulation was observed at any time investigated.

The different response in ophthalmic and tibial arteries after nasal E2 may have different explanations. It is possible to speculate that the greater response in the ophthalmic artery could depend on the higher sensitivity to E2 of this artery than the tibial artery. However, to the best of our knowledge, no data exist about the different distribution and concentration in E2 receptors as well as in the type of receptors in human arteries. Interestingly, in post-menopausal women with very low E2 levels, no differences in total ocular perfusion compared to pre-menopausal women were observed; this is evidence against the particular sensitivity of the ophthalmic artery to E2 levels12).

Alternatively, we can hypothesize that, after intranasal administration, preferential distribution of E2 to the head takes place. Accordingly, the nasal route is the known preferential route for delivering drugs to the brain and to overcome the BBB13). Drugs may reach the brain via trans-ethmoidal absorption through areas not protected by the BBB; in this case, transport may occur through the perineurium of the olfactory nerve, thereby reaching the olfactory lobe and the base of the brain. An alternative mechanism is...
a pinocytosis process so that the drug could run throughout the neurites of the olfactory nerves running in a retrograde direction. Another possible explanation is the counter-current distribution of drugs, which consists in the distribution of drugs from veins to arteries based on their different gradients; in particular, counter-current transport could occur between veins draining the nasal mucosa with a high concentration of E2 and nearby arteries such as the carotid so that E2 concentration in local arteries could be higher than in peripheral arteries11).

Our results are in agreement with literature about the vasodilatory effects of both endogenous and exogenous E214-18) on cerebrovascular and ocular circulation. Krejza et al.14) analyzed cerebrovascular impedance during the menstrual cycle and demonstrated a positive effect of E2 infusion on blood flow. Atalay et al.15) demonstrated that 6-month therapy with 17-beta E2 valerate 2 mg plus ciproterone acetate 1 mg is able to improve ocular vascular Doppler indices. Our results are also in partial agreement with those from Sahin and coworkers who demonstrated a significant decrease in the pulsatility and resistive indices of the central retinal artery but not of the ophthalmic artery in 30 healthy postmenopausal women receiving a single nasal dose of E219); methodological and technical aspects may account for this partial discrepancy.

These findings showing that nasal administration of E2 induces a significant vasodilatory effect of about one third in the opthalmic arteries suggest that this kind of administration could be an effective and suitable treatment for improving blood supply to the eyes and therefore to be clinically useful in many pathologies of the retina, such as vascular diseases, degeneration, dystrophy, and detachment20).

Our study showed some limitations. The number of patients enrolled is too small. The study needs to be improved by evaluating oral and transdermal administration of E2, comparing these to intranasal administration; however, this is only a preliminary study and we consider it as the base for further improvements.

**Conclusion**

The data from this study demonstrate that intranasal 17-beta-E2 administration at a dose of 300 µg induces a selective and more pronounced vasodilatory effect on the opthalmic arteries compared to peripheral arteries. These findings make possible to speculate that intranasal E2 administration may be employed to treat several eye diseases in which improved blood flow is required. Ad hoc clinical trials are necessary to confirm the clinical usefulness of this kind of treatment.

**Disclosures**

None to declare.

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