Effect of BQ-123, an Endothelin Antagonist, on Renal Hemodynamics, Tubular Function, Vasoactive Hormones, and Blood Pressure in Healthy Humans: A Dose Response Study

Erling B. Pedersen, Ingrid M. Thomsen, and Lene Sloth Fjordside

Background: Endothelin contributes to the maintenance of vascular tonus in both the systemic circulation and in regional vascular beds. The purpose of the study was to measure the effect of the endothelin A antagonist BQ-123 on renal hemodynamics, tubular function, vasoactive hormones, and blood pressure (BP) in healthy men.

Methods: In a randomized, placebo-controlled, double-blind dose–response study of 11 healthy men we measured the effect of BQ-123 on glomerular filtrations rate (GFR), renal plasma flow (RPF), fractional excretion of sodium (\(\text{FENa}\)), lithium clearance (\(\text{CLi}\)), BP, and plasma concentrations of renin (PRC), angiotensin II (Ang II), atrial and brain natriuretic peptides (ANP, BNP), and vasopressin (AVP). BQ-123 was infused intravenously at the rate of 0.1, 0.2, and 0.3 mg/kg for 1 h, and the effects were measured before, during, and after infusion.

Results: The GFR and RPF were not significantly changed by BQ-123. The \(\text{FENa}\) was increased (20%, medium dose), and \(\text{CLi}\) was unchanged. Systolic BP remained constant, whereas diastolic BP decreased (−6.3%, medium dose), and pulse rate increased (7.1%, medium dose). BQ-123 increased both PRC (62%, medium dose) and Ang II (70%, medium dose). The changes in \(\text{FENa}\), diastolic BP, pulse rate, and Ang II gradually increased up to medium dose, and in PRC up to high dose. The ANP, BNP, and AVP were practically unchanged by BQ-123.


Key Words: Endothelin, BQ-123, renin, aldosterone, angiotensin II, GFR, renal blood flow, sodium excretion, blood pressure, atrial natriuretic peptide, brain natriuretic peptide, vasopressin.


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blind dose–response study was done in healthy subjects using three different doses of BQ-123 in addition to placebo.

**Methods**

**Study Subjects**

Healthy subjects were included in the study. The inclusion criteria were aged 18 to 40 years, and both men and women. The exclusion criteria were: history or clinical signs of disease in the heart, lungs, liver, kidneys, brain, or endocrine organs; arterial hypertension; diabetes mellitus; neoplastic disease; daily use of medicine; alcohol abuse (defined as more than 21 drinks a week for men and more than 14 drinks a week for women); abnormal laboratory screening including B-hemoglobin and B-white cell count, plasma creatinine, aspartate aminotransferase, albumin, sodium, potassium, and urinary albumin, glucose, and hemoglobin; an abnormal electrocardiogram; pregnancy or risk of pregnancy; blood donation less than 1 month before the study; body mass index $>30$ kg/m$^2$; and unwillingness to participate in the study. The withdrawal criteria were development of one of the exclusion criteria, side effects of the test drug, and withdrawal of the acceptance to participate.

**Design**

The study was a double-blinded, placebo-controlled crossover study. All subjects received infusion of placebo and three different doses of BQ-123 on four different days with an interval of at least 14 days corresponding to a dose–response study.

**Test Substance**

BQ-123 was delivered by Clinalfa AB, Darmstadt, Germany in vials containing 5 mg and dissolved and infused intravenously in a 0.9% sodium chloride solution. The doses were 0.1 mg = 0.158 μmol/kg (low dose), 0.2 mg = 0.316 μmol/kg (medium dose), and 0.3 mg = 0.474 μmol/kg (high dose). Infusions were performed by an infusion pump and the duration was 1 h. Placebo was 0.9% sodium chloride solution.

**Sample Size**

The number of subjects needed in each group was calculated at a significance level of 5% and with a power of 90%. The minimum relevant difference was estimated to be an increase in $FE_{Na}$ of 0.40, and the corresponding SD was estimated to 0.25. The number of subjects was calculated to be 10. We included 13 subjects due to the risk of dropouts.

**Enrollment**

The study subjects were recruited by announcement and notices in public institutions and private companies.

**BQ123 / placebo**

| Urine collection |  |  |  |  |  |  |  |  |  |
|------------------|----|----|----|----|----|----|----|----|
| Blood 1          | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ |
| Blood 2          | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ |
| BP and PR        | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ | $\uparrow$ |

**FIG.1** Experimental procedure indicating time schedule with periods, time for urine collection, and blood sampling 1 for determination of $^{51}$Cr-EDTA, $^{125}$I-hippuran, sodium, and lithium; time for blood sampling 2 for determination of vasoactive hormones; and time for measurement of blood pressure (BP) and pulse rate (PR).

**Ethics**

The study was approved by the local Medical Ethics Committee and by the Danish National Board of Health. It was carried out in accordance with the Declaration of Helsinki.

**Experimental Procedure**

Each subject was instructed to take sodium chloride tablets (2 g) daily for 2 days before each study day. A 24-h urine was collected the day before the study. At 10 PM before the study day a 300-mg lithium carbonate tablet was taken orally. The subjects fasted from midnight, and they were not allowed to smoke on the study day either before or during the examination. On the study day the subjects arrived at the laboratory at 7:30 AM and 200 mL of water was given orally every 30 min from 8 h. The experimental procedure is shown in Fig.1. Seven clearance periods were performed, each of 30 min duration. Periods 1 to 3 from 9:30 to 11 AM were preinfusion control periods. During periods 4 and 5 BQ-123 or placebo was infused from 11 AM to noon. Periods 6 and 7 were postinfusion control periods from noon to 1 PM. Urine collection, blood sampling, and measurement of blood pressure (BP) and pulse rate are shown in Fig 1.

**Measurements**

The GFR and RPF were measured by a constant infusion clearance technique using $^{51}$Cr-EDTA and $^{125}$I-hippuran as reference substances, respectively, as previously described.$^8$

The PRC was measured by a commercial immunoradiometric assay (Nichols Institute Diagnostics, Geneva, Switzerland). Minimal detection level was 1.4 μIU/mL. The coefficients of variation were 2.5% (interassay) and 9.9% (intra-assay).

The Ang II, Aldo, ANP, BNP, and AVP in plasma were determined by radioimmunoassay as previously described.$^9–11$

Blood pressure was determined by a UA-743 digital BP meter (A&D Company Ltd., Tokyo, Japan). Serum and
urinary concentrations of lithium were measured by atomic absorption spectrophotometry.

Statistics

Statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL). A general linear model with repeated measures was used for comparison of the four dose groups. Parametric tests were used, but if data did not show normality we used nonparametric tests (ie, Friedman’s test for paired comparison between several groups and Wilcoxon’s signed rank test for paired comparison between two groups). Data are presented as medians with 25 to 75 quartiles or ranges. The significance level was at $P < .05$.

Results

Demographics

Thirteen healthy subjects were included in the study. Two were excluded because of an unwillingness to continue and difficulty in emptying the urinary bladder. The remaining 11 subjects fulfilled the study criteria. It comprised 9 men and 2 women, with a median age of 43 years (range 24 to 48 years), and of body mass index of 26.9 (22.9 to 29.2). Table 1 shows that no significant difference existed in clinical and laboratory data immediately before each of the four examinations.

Glomerular Filtration Rate, Renal Plasma Flow, and Renal Vascular Resistance

Table 2 shows that GFR and RPF were not significantly changed during BQ-123 infusion either during placebo, low, medium, or high doses. No significant differences existed in GFR and RPF either at baseline, during infusion, or postinfusion for GFR or RPF between the four dose regimens. The renovascular resistance (RVR) was significantly changed in the high dose groups (Table 2).

Fractional Excretion of Sodium and Lithium

Table 3 shows the effect of BQ-123 infusion on $\text{FE}_{\text{Na}}$, $\text{C}_{\text{Li}}$, and $\text{FE}_{\text{Li}}$.

Using a general linear model with repeated measures we found that $\text{FE}_{\text{Na}}$ was not significantly changed during infusion of placebo or during low dose BQ-123 infusion, that $\text{FE}_{\text{Na}}$ was increased during medium dose infusion, and that no significant change was measured during high dose infusion. During infusion of the medium dose of BQ-123 a significant increase in $\text{FE}_{\text{Na}}$ of 20% was measured in the second infusion period (infusion 30–60), and $\text{FE}_{\text{Na}}$ remained significantly elevated in the first postinfusion period (postinfusion 60–90).

The $\text{C}_{\text{Li}}$ and $\text{FE}_{\text{Li}}$ were not significantly changed by BQ-123 infusion at either of the doses used, and no significant difference was found between the dose regimens at any of the time periods.

BP and Pulse Rate

Table 4 shows the effect of BQ-123 on systolic BP, diastolic BP, and pulse rate. Systolic BP was not significantly changed in any of the groups, and no significant difference was measured between the groups for any of the time periods.

Diastolic BP was significantly reduced during infusion of BQ-123 both during the first infusion period (infusion 0 to 30) at high dose (placebo: 1.4%, low dose: $-7.4\%$,

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>112 (108–125)</td>
<td>117 (95–132)</td>
<td>117 (97–123)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>68 (55–84)</td>
<td>68 (56–75)</td>
<td>67 (62–76)</td>
</tr>
<tr>
<td>PR (beats/min)</td>
<td>52 (38–67)</td>
<td>51 (40–72)</td>
<td>54 (44–72)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.6 (63.6–99.9)</td>
<td>84.1 (64.7–98.6)</td>
<td>83.1 (63.8–99.4)</td>
</tr>
<tr>
<td>p-creatinine (µmol/L)</td>
<td>83 (60–91)</td>
<td>81 (64–99)</td>
<td>84 (66–100)</td>
</tr>
<tr>
<td>p-sodium (mmol/L)</td>
<td>140 (135–144)</td>
<td>139 (135–144)</td>
<td>138 (136–141)</td>
</tr>
<tr>
<td>p-potassium (mmol/L)</td>
<td>4.1 (3.9–4.3)</td>
<td>4.1 (3.7–4.4)</td>
<td>4.0 (3.7–4.2)</td>
</tr>
<tr>
<td>p-albumin (g/L)</td>
<td>41 (35–43)</td>
<td>42 (38–46)</td>
<td>42 (37–47)</td>
</tr>
<tr>
<td>EVF</td>
<td>0.39 (0.34–0.44)</td>
<td>0.40 (0.32–0.44)</td>
<td>0.40 (0.33–0.43)</td>
</tr>
<tr>
<td>u-sodium (mmol/24 h)</td>
<td>270 (127–429)</td>
<td>207 (118–383)</td>
<td>296 (82–392)</td>
</tr>
<tr>
<td>u-potassium (mmol/24 h)</td>
<td>80 (61–195)</td>
<td>59 (27–119)</td>
<td>94 (34–137)</td>
</tr>
</tbody>
</table>

Medians with ranges in brackets.
Table 2. Glomerular filtration rate (GFR) and renal plasma flow (RPF) in 11 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92 (87–111)</td>
<td>94 (87–105)</td>
<td>98 (83–105)</td>
<td>96 (81–105)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>91 (77–110)</td>
<td>96 (82–102)</td>
<td>89 (76–104)</td>
<td>93 (80–106)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>93 (83–102)</td>
<td>89 (83–102)</td>
<td>94 (76–108)</td>
<td>93 (73–105)</td>
</tr>
<tr>
<td>Postinfusion (60–90)</td>
<td>91 (83–105)</td>
<td>89 (77–100)</td>
<td>95 (82–105)</td>
<td>94 (73–96)</td>
</tr>
<tr>
<td>Postinfusion (90–120)</td>
<td>98 (82–107)</td>
<td>96 (85–107)</td>
<td>96 (71–109)</td>
<td>88 (81–113)</td>
</tr>
<tr>
<td><strong>RPF (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>435 (310–524)</td>
<td>435 (352–541)</td>
<td>457 (336–496)</td>
<td>419 (332–485)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>402 (305–540)</td>
<td>485 (338–523)</td>
<td>440 (356–522)</td>
<td>440 (303–507)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>428 (305–503)</td>
<td>497 (340–536)</td>
<td>440 (385–559)</td>
<td>441 (371–582)</td>
</tr>
<tr>
<td>Postinfusion (60–90)</td>
<td>431 (309–487)</td>
<td>435 (381–527)</td>
<td>466 (351–571)</td>
<td>424 (313–511)</td>
</tr>
<tr>
<td>Postinfusion (90–120)</td>
<td>395 (302–532)</td>
<td>485 (374–512)</td>
<td>466 (327–531)</td>
<td>446 (295–526)</td>
</tr>
<tr>
<td><strong>RVR (× 10³ dynes cm⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6 (6.8–13.9)</td>
<td>8.5 (6.7–11.5)</td>
<td>8.0 (6.9–12.1)</td>
<td>9.3 (8.4–13.3)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>9.0 (6.6–14.6)</td>
<td>7.9 (6.0–12.8)</td>
<td>8.5 (5.8–11.3)</td>
<td>8.3 (7.0–14.2)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>8.9 (7.3–13.3)</td>
<td>7.2 (5.8–12.5)</td>
<td>7.3 (5.9–9.9)</td>
<td>7.7* (6.1–11.4)</td>
</tr>
<tr>
<td>Postinfusion (60–90)</td>
<td>9.1 (7.4–14.1)</td>
<td>9.0 (5.8–9.5)</td>
<td>7.7 (6.1–11.0)</td>
<td>8.5 (6.9–11.5)</td>
</tr>
<tr>
<td>Postinfusion (90–120)</td>
<td>9.5 (6.7–14.4)</td>
<td>8.0 (6.1–10.1)</td>
<td>7.5 (6.1–11.3)</td>
<td>8.3 (6.3–14.1)</td>
</tr>
<tr>
<td>P (Friedman’s test)</td>
<td>.112</td>
<td>.078</td>
<td>.149</td>
<td>.024</td>
</tr>
</tbody>
</table>

All were studied four times and received infusion with BQ-123 (low dose: 0.1 mg/kg body weight, medium dose: 0.2 mg/kg, and high dose: 0.3 mg/kg), and placebo in a randomized order. Baseline was calculated as the average of three periods each of 30 min duration. Infusion was given during the two consecutive periods each of 30 min duration (infusion 0–30 and infusion 30–60). Postinfusion level was measured in two periods each of 30 min duration (postinfusion 60–90 and postinfusion 90–120). Medians with ranges in brackets.

* P < .05.

Table 3. Fractional excretion of sodium (FEₙₐ), clearance of lithium (Cₗᵢ), and fractional excretion of lithium (FEₗᵢ) in 11 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEₙₐ (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.39 (1.63–3.69)</td>
<td>2.30 (1.72–3.56)</td>
<td>1.80 (0.87–3.30)</td>
<td>2.10 (1.51–3.20)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>2.47 (1.73–4.18)</td>
<td>2.26 (1.77–3.37)</td>
<td>2.07 (0.86–4.95)</td>
<td>2.34* (1.66–3.67)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>2.62 (1.26–4.22)</td>
<td>2.40 (1.76–3.56)</td>
<td>2.16* (0.93–3.64)</td>
<td>2.27* (1.81–4.71)</td>
</tr>
<tr>
<td>Postinjection (60–90)</td>
<td>2.49 (2.07–4.20)</td>
<td>2.17 (1.67–3.60)</td>
<td>2.12* (0.98–3.37)</td>
<td>2.19 (1.09–3.02)</td>
</tr>
<tr>
<td>Postinjection (90–120)</td>
<td>2.37 (1.62–3.75)</td>
<td>2.21 (1.53–3.15)</td>
<td>2.04 (0.99–2.79)</td>
<td>2.02 (1.06–2.69)</td>
</tr>
<tr>
<td>P (Friedman’s test)</td>
<td>.070</td>
<td>.122</td>
<td>.007</td>
<td>.319</td>
</tr>
<tr>
<td><strong>Cₗᵢ (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30 (21–43)</td>
<td>29 (22–40)</td>
<td>28 (22–36)</td>
<td>28 (16–41)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>26 (22–48)</td>
<td>29 (23–36)</td>
<td>27 (14–36)</td>
<td>30 (23–36)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>31 (13–40)</td>
<td>29 (20–36)</td>
<td>29 (19–48)</td>
<td>32 (22–40)</td>
</tr>
<tr>
<td>Postinjection (60–90)</td>
<td>31 (19–46)</td>
<td>27 (22–37)</td>
<td>28 (23–36)</td>
<td>24 (20–36)</td>
</tr>
<tr>
<td>Postinjection (90–120)</td>
<td>32 (20–40)</td>
<td>30 (22–35)</td>
<td>26 (15–35)</td>
<td>27 (15–32)</td>
</tr>
<tr>
<td><strong>FEₗᵢ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>33 (21–42)</td>
<td>31 (22–40)</td>
<td>30 (22–37)</td>
<td>28 (15–45)</td>
</tr>
<tr>
<td>Infusion (0–30)</td>
<td>31 (20–43)</td>
<td>31 (23–41)</td>
<td>29 (16–48)</td>
<td>29 (23–46)</td>
</tr>
<tr>
<td>Infusion (30–60)</td>
<td>37 (14–40)</td>
<td>31 (22–41)</td>
<td>33 (22–54)</td>
<td>37 (24–48)</td>
</tr>
<tr>
<td>Postinjection (60–90)</td>
<td>35 (18–46)</td>
<td>30 (22–39)</td>
<td>32 (22–38)</td>
<td>28 (23–39)</td>
</tr>
<tr>
<td>Postinjection (90–120)</td>
<td>32 (20–40)</td>
<td>31 (22–37)</td>
<td>28 (23–36)</td>
<td>29 (17–37)</td>
</tr>
</tbody>
</table>

All were studied four times and received infusion with BQ-123 (low dose: 0.1 mg/kg body weight, medium dose: 0.2 mg/kg, and high dose: 0.3 mg/kg), and placebo in a randomized order. Baseline was calculated as the average of three periods each of 30 min duration. Infusion was given during the two consecutive periods each of 30 min duration (infusion 0–30 and infusion 30–60). Postinfusion level was measured in two periods each of 30 min duration (postinfusion 60–90 and postinfusion 90–120). Medians with ranges in brackets.

* P < .05.

medium dose: −2.9%, and high dose: −4.4%, P < .05), and in the second infusion period (infusion 30 to 60) at both medium and high dose (placebo: 0%, low dose: −8.8%, medium dose: −6.3%, P < .05, and high dose: −7.4%, P < .05). No significant difference was measured between the groups for any of the periods. In the two postinfusion periods diastolic BP remained reduced at low, medium, and high doses of B-123.
Pulse rate increased slightly but significantly during infusion of BQ-123 during infusion 0 to 30 at medium dose (placebo: 0%, low dose: 1.9%, medium dose: 7.1%, P = 0.05, and high dose: 2%) and infusion 30 to 60 at low, medium, and high doses (placebo: 0%, low dose: 5.5%, P = 0.05, medium dose: 7.1%, P = 0.05, and high dose: 11%, P = 0.05). In the two postinfusion periods pulse rate remained significantly elevated at low, medium, and high doses of BQ-123.

**Renin, Angiotensin II, and Aldosterone**

Table 5 shows the effect of BQ-123 infusion on PRC, Ang II, and Aldo.

The PRC was not significantly changed after placebo either just after infusion (25%, P = 0.159) or at the end of the experiment (13%, P = 0.336). The BQ-123 infusion resulted in a significant increase in Ang II at low and medium doses, and a borderline significant increase at the high dose. Just after the infusion and at the end of the experiment the increases were 20% (P = 0.072) and 30% (P = 0.010), respectively, in the low dose group. The corresponding values in the medium dose group were 40% (P = 0.120) and 70% (P = 0.014), and in the high dose group 20% (P = 0.159) and 50% (P = 0.358). The baseline levels of Ang II were the same at the four examinations (P = 0.134). Just after the infusion Ang II was the same at the four examinations (P = 0.289), but at the end of the experiment there was a borderline significance (P = 0.064). There was a gradual increase in Ang II up to the medium dose of BQ-123.

The Aldo was not significantly changed by BQ-123 infusion and no significant differences were measured between the dose groups.

**Atrial Natriuretic Peptide, Brain Natriuretic Peptide, and Vasopressin**

Table 5 shows the effect of BQ-123 infusion on ANP, BNP, and AVP.

The ANP was not significantly changed after placebo and the low dose, but ANP was significantly reduced after the medium dose and borderline after the high dose. How-
ever, the changes were small, and there was no significant difference between the four dose groups.

The BNP and AVP were not significantly changed by BQ-123 infusion and no significant difference was measured between the dose groups.

Discussion

The present study showed that infusion of the endothelin antagonist BQ-123 increased urinary excretion of sodium despite a decrease in diastolic BP, and an increase in renin and angiotensin II in plasma.

In healthy humans infusion of endothelin decreased GFR, RPF and urinary sodium excretion, and increased BP.\(^{12–15}\) The effect of endothelin on renal hemodynamics and urinary sodium excretion could be blocked completely or partially by endothelin receptor antagonists.\(^{14,15}\) In healthy humans infusion studies with BQ-123 have shown that ETA receptors contribute substantially to the vasoconstriction induced by Ang II in the systemic and renal circulation.\(^{16}\) In addition, blockade of the ETA receptor with BQ-123 attenuated the systemic and renal hemodynamic effect of inhibition of the nitric oxide synthase.\(^{17,18}\)

Apparently, the vasoconstrictor effect of ET, the renin-angiotensin system, and the sympathetic nervous system is antagonized by nitric oxide-induced vasodilation in the renal vascular bed. In the present study blockade of the ET\(_A\) receptor alone with BQ-123 did not change either GFR or RPF during placebo or at the three different doses of BQ-123, and this is in agreement with a previous study.\(^{14}\) Thus, during baseline conditions ETA does not contribute much to the renal vascular tone. However, BQ-123 has a renal effect because we measured an increase in renal sodium excretion.

We measured a decrease in diastolic BP and an increase in pulse rate after infusion of BQ-123 in low dose, and both during and after infusion at medium and high doses, whereas no effect was seen during placebo treatment. This effect on the systemic circulation is in agreement with many studies of the effect of either parenteral or oral ETA antagonism.\(^{19,20}\) In healthy humans local infusion of BQ-123 resulted in vasodilatation of the forearm vascular bed,\(^1\) and reduced peripheral vascular resistance,\(^6\) and

| Table 5. Plasma concentrations of renin (PRC), angiotensin II (Ang II), aldosterone (Aldo) atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and vasopressin (AVP) in 11 healthy subjects |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Placebo         | Low Dose        | Medium Dose     | High Dose       |
| PRC (µIU/mL)                   |                 |                 |                 |                 |
| Just after infusion            | 11 (5–19)       | 18* (7–26)      | 14* (7–29)      | 19* (3–25)      |
| One h after infusion           | 11 (5–19)       | 19* (8–29)      | 21* (9–30)      | 24* (2–31)      |
| P (Friedman’s test)            | .131            | .002            | .000            | .003            |
| Ang II (pmol/L)                |                 |                 |                 |                 |
| Before infusion                | 8 (1–16)        | 10 (3–24)       | 10 (2–22)       | 10 (2–40)       |
| Just after infusion            | 10 (1–24)       | 12 (4–28)       | 14 (2–22)       | 12 (3–38)       |
| One h after infusion           | 9 (2–18)        | 13* (4–34)      | 17* (2–23)      | 15 (3–30)       |
| P (Friedman’s test)            | .446            | .017            | .015            | .052            |
| Aldo (pmol/L)                  |                 |                 |                 |                 |
| Before infusion                | 59 (34–143)     | 63 (32–161)     | 68 (26–194)     | 65 (33–170)     |
| Just after infusion            | 60 (25–93)      | 64 (20–95)      | 60 (29–160)     | 80 (28–176)     |
| One h after infusion           | 61 (40–81)      | 57 (34–114)     | 77 (37–175)     | 77 (26–166)     |
| P (Friedman’s test)            | .103            | .366            | .741            | .559            |
| ANP (pmol/L)                   |                 |                 |                 |                 |
| Before infusion                | 4.6 (2.3–11.5)  | 5.6 (4.3–8.6)   | 5.9 (3.4–8.6)   | 4.9 (3.6–12.0)  |
| Just after infusion            | 5.0 (2.5–12.2)  | 5.6 (3.2–7.8)   | 4.9* (3.7–7.4)  | 4.7 (2.7–10.3)  |
| One h after infusion           | 5.0 (2.3–12.4)  | 4.8* (2.5–8.1)  | 5.2* (2.6–7.0)  | 4.0 (2.3–10.0)  |
| P (Friedman’s test)            | .913            | .266            | .002            | .052            |
| BNP (pmol/L)                   |                 |                 |                 |                 |
| Before infusion                | 2.6 (0.8–7.8)   | 2.1 (1.4–5.0)   | 2.2 (0.9–3.7)   | 1.8 (0.9–7.5)   |
| Just after infusion            | 3.0 (0.8–8.0)   | 1.9 (1.1–4.7)   | 2.1 (0.9–3.7)   | 1.8 (1.2–7.0)   |
| One h after infusion           | 2.8 (0.9–8.3)   | 1.8 (1.3–4.2)   | 1.9 (0.8–3.3)   | 1.7 (1.3–7.7)   |
| P (Friedman’s test)            | .146            | .227            | .590            | .388            |
| AVP (pmol/L)                   |                 |                 |                 |                 |
| Before infusion                | 0.6 (0.4–0.8)   | 0.7 (0.5–1.1)   | 0.7 (0.5–1.1)   | 0.7 (0.5–0.9)   |
| Just after infusion            | 0.7 (0.4–0.8)   | 0.7 (0.4–0.9)   | 0.6 (0.6–0.8)   | 0.7 (0.4–0.9)   |
| One h after infusion           | 0.7 (0.4–0.8)   | 0.7 (0.4–1.1)   | 0.6 (0.5–1.0)   | 0.7 (0.5–1.4)   |
| P (Friedman’s test)            | .140            | .798            | .205            | .922            |

All were studied four times and received infusion with BQ-123 (low dose: 0.1 mg/kg body weight, medium dose: 0.2 mg/kg, and high dose: 0.3 mg/kg), and placebo in a randomized order. Blood samples were drawn just before infusion, just after infusion, and 1 hour after the infusion had stopped. Medians with ranges in brackets. * P < .05.
endogenous ET was suggested to contribute to the regulation of basal vascular tone in healthy humans. In contrast, resting forearm blood flow was not significantly changed in healthy subjects after BQ-123 infusion according to another study, but the infusion time was very short (only a few minutes), and thus much less than in the present and many other studies. Our results show that basal tone in the systemic vascular bed is partially dependent on ET stimulation.

In the present study the total dose of BQ-123 was based on body weight as in some other studies. However, in several studies a fixed dose was used independent of the participants’ body weight. The infusion rates of BQ-123 in the present study were in between the low and high infusion rates used by Godard et al., two to six times higher than the doses used by Schmetterer et al. and Schmidt et al., corresponding to the three dose levels used in the present dose–response study, and several times higher than the very low infusion rates used by Montanari et al. The total dose of BQ-123 in the present low dose regimen was lower than in some studies, and approximately the same as in another study. However, it was clearly higher than the doses used by Montanari et al. The present study was designed as a dose–response study to determine the effect of BQ-123. It cannot be excluded that the natriuresis demonstrated in our study could be attributed to a possible displacement of endogenous ET from the ETα receptors allowing an activation of the ETβ receptors to produce more nitric oxide and thus reduce renal tubular sodium reabsorption.

We measured an increase in FENa during BQ-123 infusion in the present study using the medium dose. No effect was seen during placebo and low dose infusion, and during high dose infusion the effect was less pronounced. The changes in FENa were relatively small. The baseline level at the medium dose was numerically lower, although not statistically significant, than baseline levels at placebo, low, and high doses. However, FENa also increased at the high dose infusion when the baseline level was numerically higher. A natriuretic effect of BQ-123 has previously been demonstrated in some studies. We measured an unchanged GFR and lithium clearance during BQ-123 infusion. Thus, the natriuresis during infusion cannot be attributed to changes in filtration or the proximal tubular function. It seems most likely that the effect is mediated in the distal part of the nephron. The RVR tended to decrease during BQ-123 infusion, but a significant decrease was only measured during high dose infusion, and the changes were small and might be by chance. A decrease in RVR might be responsible for natriuresis, but a significant increase in FENa was only measured in the medium dose regimen, during which RVR was unchanged. Both renin and Ang II in plasma were clearly increased during BQ-123 infusion, especially during medium and high doses. Divergent results exist regarding the effect of BQ-123 on renin secretion. Our results show that the natriuretic effect of BQ-123 overrides the sodium retaining effect of increased activity in the renin-angiotensin system. The lesser effect on urinary sodium excretion by the highest dose of BQ-123 most likely can be attributed to a more marked counter-regulatory effect of the renin-angiotensin system or by a more marked decrease in BP at the highest dose.

The BNP and AVP were unchanged, and the changes in ANP were very modest and might be by chance.

The sodium balance influences both the systemic and the hemodynamic response to intervention in the nitric oxide system and thus possibly also the effect of BQ-123. It was not the aim to perform the study either during sodium loading or sodium depletion. However, we intended to avoid sodium depletion by giving sodium chloride tablet (2 g daily) for 2 days before each examination. Urinary sodium excretion did not deviate significantly between the four dose groups and the medians were around 200 to 300 mmol/24 h, indicating that sodium balance for each subject was the same at the four examinations.

In conclusion, our results show that endothelin plays a role during baseline conditions both for systemic vascular tone and the regulation of renal sodium excretion, and that blockade of the ETα receptor apparently can resist and to some extent antagonize the effects of the renin-angiotensin system on BP regulation and sodium balance.

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References


