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A. Wiecek · D. Fliser · M. Nowicki · E. Ritz

Effect of moxonidine on urinary electrolyte excretion and renal haemodynamics in man

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Abstract Moxonidine and related compounds have been recently introduced into antihypertensive therapy. It is thought that these drugs exert their blood pressure lowering effect through interaction with non-adrenergic receptors in the central nervous system, i.e. imidazoline receptors, although the contribution of specific interaction with α_2-receptors is still under debate. Imidazoline receptors have recently been documented in the renal proximal tubule. In experimental studies, interaction of imidazolines with these receptors decreased the activity of the Na^+/H^+ antiporter and induced natriuresis. To quantitate the effect of the imidazoline receptor agonist moxonidine on renal sodium handling and renal haemodynamics in man, we examined ten healthy normotensive males (aged 25 ± 4 years) in a double blind placebo-controlled study using a crossover design. Subjects were studied on a standardized salt intake (50 mmol per day). On the 7th and 10th study day they were randomly allocated to receive either i.v. placebo or i.v. 0.2 mg moxonidine. Urinary electrolyte excretion, lithium clearance (as an index of proximal tubular sodium handling), glomerular filtration rate (GFR), effective renal plasma flow (ERPF), renal vascular resistance (RVR), mean arterial blood pressure (MAP), plasma renin activity (PRA) and plasma noradrenaline (NA) levels were assessed. Injection of moxonidine did not increase fractional sodium excretion or lithium clearance. Specifically, antinatriuresis was not observed after injection of moxonidine despite a significant decrease in MAP from 91 to 85 mmHg and a significant increase in PRA. MAP and PRA did not change with administration of placebo. Injection of moxonidine did not affect GFR and RVR; ERPF decreased slightly but not significantly. Acute administration of 0.2 mg i.v. moxonidine decreased blood pressure in healthy volunteers on standardized salt intake, but did not affect natriuresis, proximal tubular sodium reabsorption or glomerular filtration rate. The absence of an antinatriuretic response despite a decrease in blood pressure suggests a direct facilitation of natriuresis by moxonidine.

Key words Moxonidine, Renal haemodynamics; imidazoline receptors, natriuresis, blood pressure, healthy volunteers

A. Wiecek · M. Nowicki
Department of Internal Medicine, University of Katowice, Katowice, Poland

D. Fliser · E. Ritz (✉)
Department of Internal Medicine, Ruperto-Carola University Heidelberg, Bergheimer Strasse 56a, D-69115 Heidelberg, Germany

Moxonidine and related compounds (i.e. imidazolines) have been recently introduced into antihypertensive therapy. It is thought that these drugs exert their blood pressure lowering effect through interaction with non-adrenergic receptors in the central nervous system, i.e. imidazoline receptors, which are located in the nucleus reticularis lateralis (NRL) of the medulla oblongata [1, 2]. Several imidazolines such as clonidine and rilmenidine bind to these receptors and when injected into the NRL of laboratory animals they lower blood pressure in a dose-dependent fashion [3–5]. However, a contribution of specific interaction with α_2-adrenoceptors to the blood pressure lowering effect of moxonidine is still under debate [6]. Comparative studies have shown that moxonidine lowers blood pressure in patients with primary hypertension as effectively as clonidine, prazosin, atenolol and nifedipine, on the one hand, and has fewer side effects than the less specific α-adrenoceptor agonist clonidine on the other hand [7–12].

Recently, imidazoline receptors have also been found in some kidney structures, i.e. proximal tubules [13] and renal medulla [14]. In experimental studies, stimulation of renal α_2-adrenergic receptors increased the activity of the Na^+/H^+ antiporter in the proximal tubule [15, 16], whereas interaction of imidazolines with the

renal imidazoline receptive sites decreased its activity [17]. A decrease in the antiporter's activity is thought to result in a decrease in net sodium reabsorption. In agreement with this concept, imidazolines induce natriuresis in laboratory animals [18]. It has therefore been proposed that the antihypertensive effect of imidazolines, e.g. moxonidine, is mediated in part through interaction with renal imidazoline receptive sites, although the possibility of natriuresis as a consequence of decreased sympathetic tone has not been excluded. In humans the effect of moxonidine on natriuresis, if any, has not been documented.

To pursue this issue we examined the effect of moxonidine on urinary sodium excretion, lithium clearance (as an index of proximal tubular sodium handling) and renal haemodynamics in man. For this purpose, healthy volunteers were studied on a standardized salt intake using a double-blind placebo-controlled crossover design.

Materials, methods and subjects studied

Volunteers

The study was approved by the Ethics Committee of the University of Heidelberg. Ten healthy normotensive male subjects [mean age, 25 (4) years] took part in the study. Written informed consent was obtained from all participants.

Protocol

A crossover double-blind placebo-controlled design was chosen. Prior to the study, the volunteers' health status was examined and routine laboratory tests were carried out. Thereafter volunteers received a standardized salt diet for 10 days. All subjects received a precooked deep-frozen diet containing 50 mmol Na^+ (confirmed by duplicate analysis). Compliance with the diet was monitored by regular measurements of sodium in 24-h urine collections. After equilibration, i.e. from the 3rd day of the diet onward, maximal deviation of 24-h urinary sodium excretion from the calculated intake was 10 mmol. A steady state of sodium excretion was reached by approximately the 4th day of the study, thereafter sodium excretion was stable, i.e. 52.4 (4.9) mmol per 24 h on the 6th study day.

The volunteers were admitted to the clinic on the evening of the 6th and 9th days. They received 450 mg (12 mmol) lithium carbonate at 2200 hours (in order to measure the lithium clearance) and examinations were carried out with the volunteers in the supine position in a quiet room on the next day (7th and 10th study day) following an overnight fast. After they had emptied their bladders, a sham injection was given at 0800 hours on both study days in order to assess and compare baseline urinary electrolyte excretion (from 0800 hours to 1000 hours). At 1000 hours (using random numbers), the subjects were assigned to receive a bolus injection of either placebo or 0.2 mg moxonidine. Thereafter they collected urine from 1000 hours to 1200 hours, from 1200 hours to 1400 hours and from 1400 hours to 1600 hours. Urinary excretion of sodium, potassium, calcium, phosphate and lithium was measured. To achieve a steady state of urine flow, volunteers drank a quantity of tap water which matched the urine volume in the preceding period. Plasma sodium and lithium concentrations were determined at 0800 hours, 1000 hours, 1200 hours, 1400 hours and 1600 hours for calculations of fractional sodium excretion and lithium clearance. On both study days glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were examined using steady-state inulin (C_{in}) and para-aminohippurate (C_{PAH}) infusion techniques. In brief, a priming dose of 1500 mg inulin $\cdot m^{-2}$ (Inutest, Laevosan, Austria) and 500 mg PAH $\cdot m^{-2}$ (Nephrotest, Biologische Arbeitsgemeinschaft, Germany) was given at 0800 hours. The bolus injection was followed by continuous infusions of inulin (10 mg $\cdot m^{-2} \cdot min^{-1}$) and PAH (8 mg $\cdot m^{-2} \cdot min^{-1}$) maintained with ultraprecise pumps (Perfusor FT, Braun Melsungen, Germany). After a 90-min equilibration period, blood samples for measurements of GFR and ERPF were taken at regular intervals until 1400 hours. In parallel, blood pressure and heart rate were measured at regular intervals throughout with the volunteers in the supine position. Blood samples for estimation of noradrenaline (NA) levels and plasma renin activity (PRA) were taken at 1000 hours (baseline) and 1200 hours (postinjection).

Measurements and calculations

Plasma and urine chemistry were measured with standard laboratory methods (autoanalyser), electrolytes with flame photometry, Li^+ plasma and urine concentrations with atomic adsorption photometry, PRA with RIA and NA levels with high-performance liquid chromatography (HPLC) [19]. Inulin was measured enzymatically using inulinase as described by Kühnle et al. [20] and para-aminohippurate photometrically according to the method of Bratton and Marshall [21]. Mean arterial blood pressure (MAP) and heart rate (HR) were measured with a non-invasive oscillometric technique (Dinamap, Criticon, USA).

The fractional excretion of sodium (FE_{Na}) was calculated as the ratio between urinary Na^+ excretion rate ($U_{Na} \times V$) and filtered Na^+ load (GFR $\times$ plasma Na^+). The lithium clearance (CL_{Li}) was calculated from the plasma and urinary lithium concentrations. The fractional reabsorption of sodium in the proximal tubule, i.e. the fractional proximal reabsorption of sodium (FDR_{Na}), was calculated as $FPR_{Na} = 1-(CL_{Li}/GFR)$. The fractional reabsorption of sodium in the distal tubule, i.e. the fractional distal reabsorption of sodium (FDR_{Na}) was calculated as $FDR_{Na} = 1-(CL_{Na}/CL_{Li})$, where CL_{Na} is the sodium clearance [22]. CL_{in} and CL_{PAH} were calculated from the delivered dose: $CL = (Ir \times Ic)/Sc$; where CL is the clearance, Ir is the infusion rate (ml $\cdot min^{-1}$), Ic is the concentration of the analyte in the infusion fluid (mg $\cdot ml^{-1}$) and Sc is the serum concentration of the analyte (mg $\cdot ml^{-1}$). Filtration fraction (FF) was calculated as the ratio CL_{in}/CL_{PAH} and renal vascular resistance (RVR) using the equation $RVR = [(MAP-12) \times 723/ERPF] \times (1-hct)$; where hct is haematocrit.

Statistical analysis

The primary end point of the study was the difference in fractional urinary sodium excretion (FE_{Na}) after injection of moxonidine and injection of placebo. Statistical significance of differences was evaluated with the two-factorial analysis of variance (ANOVA) using the SAS system. A P value of < 0.05 was considered as statistically significant. All other data (i.e. blood pressure, heart rate, renal haemodynamics, lithium clearance, PRA and NA levels) were analysed with ANOVA. Data are given as means with SD.

Results

Urinary electrolyte excretion and lithium clearance in volunteers on standardized salt intake after administration of placebo and moxonidine

Table 1 shows baseline (0800 hours – 1000 hours) and post-treatment (1000 hours – 1600 hours) mean urinary

Table 1 Excretion rates and tubular handling of sodium at baseline and postinjection in ten volunteers on standardized salt (50 mmol per day) intake. Placebo or moxonodine were injected at 1000 hours

Time (h)	0800–1000 hours	1000–1200 hours	1200–1400 hours	1400–1600 hours
Urine flow ($ml \cdot min^{-1}$)				
Placebo	3.7 (1.7)	3.8 (1.9)	3.8 (1.9)	3.7 (1.8)
Moxonidine	3.4 (1.4)	3.7 (1.3)	3.3 (1.6)	3.6 (1.9)
Na^+ excretion ($mmol \cdot min^{-1}$)				
Placebo	0.07 (0.04)	0.09 (0.05)	0.10 (0.05)	0.10 (0.06)
Moxonidine	0.07 (0.05)	0.09 (0.07)	0.09 (0.07)	0.10 (0.07)
FE_{Na} (%)				
Placebo	0.5 (0.3)	0.6 (0.3)	0.7 (0.4)	0.6 (0.4)
Moxonidine	0.5 (0.3)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)
CL_{LI} (%)				
Placebo	17 (8)	14 (3)	14 (4)	13 (4)
Moxonodine	15 (7)	14 (5)	13 (3)	16 (8)
FPR_{Na} (%)				
Placebo	84 (7)	88 (3)	88 (4)	–
Moxonodine	87 (5)	88 (3)	88 (3)	–
FDR_{Na} (%)				
Placebo	97 (2)	95 (2)	95 (2)	–
Moxonodine	96 (2)	95 (3)	95 (4)	–

FE_{Na}, fractional excretion of sodium; C_{LI}, lithium clearance; FPR_{Na}, fractional proximal reabsorption of sodium; FDR_{Na}, fractional distal reabsorption of sodium

Table 2 Excretion rates of potassium (K^+), calcium (Ca^{2+}) and phosphate (P^{2-}) in ten healthy volunteers on standardized salt intake. Placebo or moxonodine were injected at 1000 hours

Time (h)	0800–1000 hours	1000–1200 hours	1200–1400 hours	1400–1600 hours
K^+ ($mmol \cdot 2\ h^{-1}$)				
Placebo	11.7 (6.1)	10.7 (2.9)	10.1 (2.4)	8.3 (4.2)
Moxonodine	13.4 (6.6)	11.0 (3.1)	11.2 (3.5)	8.6 (3.1)
Ca^{2+} ($mmol \cdot 2\ h^{-1}$)				
Placebo	0.5 (0.2)	0.5 (0.2)	0.6 (0.3)	0.6 (0.2)
Moxonodine	0.4 (0.1)	0.5 (0.2)	0.5 (0.3)	0.5 (0.3)
P^{2-} ($mmol \cdot 2\ h^{-1}$)				
Placebo	1.4 (0.7)	1.1 (0.4)	1.2 (0.5)	1.3 (0.3)
Moxonodine	1.3 (0.5)	1.3 (0.7)	1.2 (0.6)	1.3 (0.7)

sodium excretion rate, fractional sodium excretion (FE_{Na}), fractional proximal (FPR_{Na}) and distal (FDR_{Na}) reabsorption of sodium and lithium clearance in volunteers on a standardized salt diet. There were no significant differences with respect to these parameters after injection of moxonidine as compared with placebo. The mean urinary excretion rates of potassium, calcium and phosphate are further shown in Table 2. They did not differ between placebo and moxonidine treatment periods.

Arterial blood pressure, heart rate and renal haemodynamics in volunteers on standardized salt intake after administration of placebo and moxonidine

Mean MAP decreased after injection of moxonidine, but not after injection of placebo, i.e. within the 1st h after drug administration (Fig. 1). The difference between preinjection and postinjection MAP with moxonidine was significant, but not with placebo treatment. In contrast, no significant change in mean heart rate was observed with moxonidine and placebo treatment. The mean GFR did not change after administration of moxonidine, whereas mean ERPF tended to decrease (Fig. 2); the difference was not significant. Since both MAP and ERPF decreased, no significant change in their ratio, i.e. mean RVR, was observed after moxonidine injection as compared with placebo.

Noradrenaline levels and plasma renin activity

Mean plasma NA levels decreased significantly after administration of moxonidine, but not so with placebo (Table 3). In contrast, mean PRA increased significantly after moxonidine injection; it stayed virtually unchanged with the placebo time control.

Discussion

The present placebo-controlled study in healthy volunteers does not demonstrate a significant effect of acute i.v. moxonidine administration on net urinary sodium excretion rate (as an index of overall renal

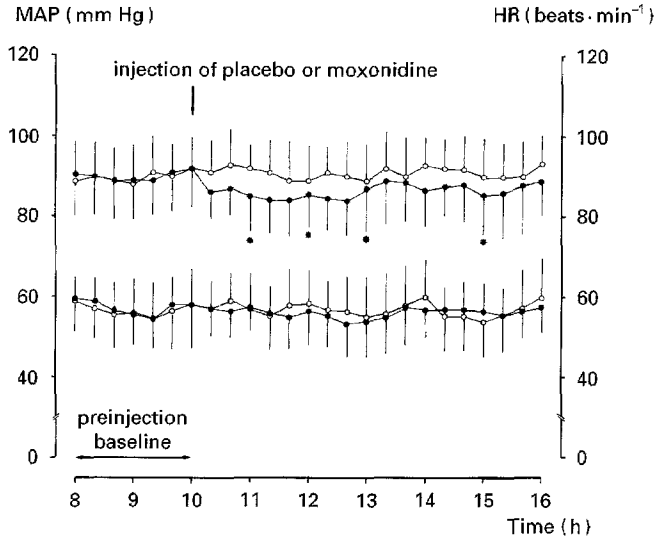

Fig. 1 Mean arterial blood pressure (*MAP* upper trace) and heart rate (*HR* lower trace) after injection of placebo or moxonidine (at 1000 hours) in ten volunteers on standardized salt intake (50 mmol per day). *open circles* placebo, *closed circles* moxonidine, $*P < 0.05$ comparing hourly postinjection values with preinjection baseline at 1000 hours

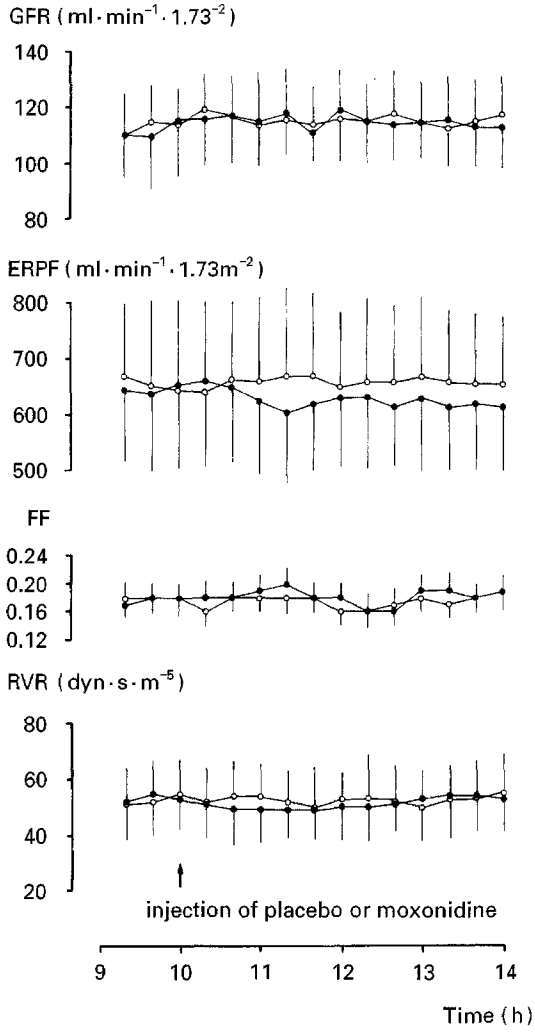

Fig. 2 Mean glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF) and renal vascular resistance (RVR) after injection of placebo or moxonidine (at 1000 hours) in ten volunteers on standardized salt intake (50 mmol per day). *open circles* placebo, *closed circles* moxonidine

handling of Na^+) and lithium clearance (as an index of proximal tubular Na^+ handling). The absence of changes in lithium clearance is in line with the absence of an effect on phosphate excretion, an index of proximal tubular bulk reabsorption. The finding of unchanged natriuresis is unexpected in view of (1) the small but definite fall in systemic mean arterial blood pressure, (2) the tendency for lower renal perfusion (ERPF) and (3) the increase in plasma renin activity, all of which should cause antinatriuresis. Activation of the renin-angiotensin system is notable in view of the decreased NA levels and unchanged urinary Na^+ excretion; our observations suggest marked stimulation of the intrarenal baroreceptors. It is suggested that unchanged natriuresis is inappropriately high relative to the above factors. Sympathetic activation facilitates tubular Na^+ reabsorption [23]. Conversely, inappropriately high natriuresis in our volunteers may have been favoured by withdrawal of sympathetic tone as indicated by a significant decrease in plasma NA concentration. We cannot exclude the alternative possibility that inappropriate natriuresis after moxonidine was due to direct interaction with renal imidazoline receptors.

Several points in the present study deserve more detailed comment. Little is known concerning the action of moxonidine on renal haemodynamics in humans. Frisk-Holmberg and Plänitz [24] found no change in creatinine clearance (a crude measure of GFR) in patients with primary hypertension after 3 weeks of moxonidine treatment with 0.6 mg per day. In the present study, acute administration of an effective dose of moxonidine to volunteers on a relatively low sodium diet with sympathetic stimulation, as documented by high NA levels, did not change RVR. ERPF tended to decrease in parallel with the fall in blood pressure, but GFR remained stable. The finding of unchanged GFR after acute moxonidine administration contrasts with the observation of a modest decline in GFR after acute administration of other sympathoinhibitor agents, e.g. guanabenz, clonidine and α-methyldopa, in hypertensive patients [25, 26].

The time course of the action of moxonidine was rapid. We observed a decrease of MAP in our volunteers within 20 min after injection. In parallel, NA levels had decreased by 2 h after moxonidine injection. Consequently, although the time of observation in the present study was short, it is unlikely that we missed a net natriuretic effect of moxonidine because of a too short investigation period. The rapid decrease in NA contrasts with observations in studies examining moxonidine per os [27] and may be explained by (1)

Table 3 Baseline and postinjection mean plasma NA levels and PRA in ten volunteers on standardized salt intake. Placebo or moxonodine were injected at 1000 hours

Time (h)	1000 hours (baseline)	1200 hours (2 h after injection)
NA (nmol/l)		
Placebo	1.05 (0.31)	1.02 (0.24)
Moxonidine	1.03 (0.44)	0.86 (0.25)*
PRA (ng·AngI·ml^{-1}h^{-1})		
Placebo	1.17 (0.49)	1.22 (0.54)
Moxonidine	1.17 (0.56)	1.50 (0.76)*

*$P < 0.05$ – baseline vs postinjection values compared with ANOVA

sympathetic prestimulation and an increase in NA levels as a result of the relatively low sodium diet and (2) rapid onset of action as a result of i.v. injection. The mean NA concentration was 1.05 (0.31) μmol·l^{-1} on a sodium intake of 50 mmol per day as compared with 0.76 (0.19) μmol·l^{-1} on 200 mmol Na^+ per day [28].

In the present study a rather small dose of moxonidine was acutely injected. We had chosen a dose which did not lower blood pressure in healthy volunteers on higher sodium intake when given orally or i.v. [29, 30]. This small dose was chosen in order to prevent a too marked fall in blood pressure which might confound interpretation of measurements of natriuresis and renal haemodynamics. The blood pressure lowering effect of moxonidine in our study may have been increased by the low content of sodium in the diet. It is of note that in patients with primary hypertension the antihypertensive action of moxonidine is potentiated by concomitant administration of a diuretic [31]. This finding is in line with the results of our study and further supports the conclusion that the antihypertensive effect of moxonidine was enhanced by negative salt balance. In view of prestimulation of PRA by the diet (1.2 (0.6) ngAngI·h^{-1}·ml^{-1} on 50 mmol sodium intake per day vs 0.3 (0.1) ngAngI·h^{-1}·ml^{-1} on 200 mmol Na^+ per day [28]), it is particularly noteworthy that a decrease in blood pressure did not provoke antinatriuresis.

Treatment with centrally sympathoinhibitor agents, e.g. guanabenz, clonidine or α-methyldopa, is known to result in an acute net gain of weight [25, 26]. This finding has been related to stimulation of renal α_2-adrenergic receptor sites which in turn activate the Na^+/H^+ antiporter and induce sodium reabsorption and retention [15, 16]. In contrast we did not observe an acute change in net urinary sodium excretion after moxonidine. It is obvious that moxonidine has actions on tubular handling of sodium which differ from those of other centrally sympathoinhibitor agents. All of them reduce efferent sympathetic traffic and the uniform withdrawal of sympathetic tone in the kidney cannot explain the contrasting effects on tubular sodium handling.

In conclusion, acute administration of the imidazoline moxonidine (0.2 mg by injection) decreases blood pressure in healthy volunteers on standardized salt intake, but does not significantly affect natriuresis, proximal tubular sodium transport or renal vascular resistance. The absence of an antinatriuretic response despite lowering of blood pressure is compatible with the possibility that moxonidine facilitates natriuresis by direct interaction with imidazoline receptors and/or by withdrawal of sympathetic tone.

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