Metoclopramide Stimulates Kaliuresis During Felodipine Without Affecting Its Natriuresis

Henk W. van Hamersvelt, Jack F.M. Wetzels, Robert A.P. Koene, Frans Th.M. Huysmans

Abstract Calcium entry blockers such as felodipine induce natriuresis without a parallel rise of potassium excretion. Previous studies with exogenous aldosterone and felodipine have suggested that the absence of kaliuresis might be explained by a felodipine-induced inhibition of aldosterone release. The natriuresis with calcium entry blockers could not be attributed to a similar mechanism but might be due to the stimulation of intrarenal natriuretic systems such as the dopaminergic system. We studied whether the selective dopamine antagonist metoclopramide prevents the natriuresis with low and therapeutic felodipine doses and whether metoclopramide-induced aldosterone release promotes kaliuresis with felodipine. Twelve healthy male volunteers participated in a randomized, placebo-controlled, crossover study comparing felodipine infusion during metoclopramide with felodipine alone. Metoclopramide had no significant influence on the pronounced and dose-dependent increases of renal plasma flow and urinary sodium excretion with felodipine. Metoclopramide increased plasma aldosterone concentration from 0.17±0.03 to 0.60±0.14 nmol/L, and subsequent felodipine infusion clearly increased urinary potassium excretion by 23±6 and 35±8 μmol/min (low and therapeutic doses, respectively). In contrast, potassium excretion remained stable with felodipine alone (+5±2 and +7±5 μmol/min, respectively). In conclusion, the natriuretic action of calcium entry blockers cannot be blocked by the selective dopamine antagonist metoclopramide. This natriuresis is accompanied by kaliuresis only in the presence of elevated endogenous aldosterone concentrations. The ability of calcium entry blockers to prevent a rise of plasma aldosterone thus seems essential for the prevention of urinary potassium losses. (Hypertension. 1994;24:633-639.)

Key Words • calcium channel blockers • felodipine • metoclopramide • aldosterone • natriuresis • kaliuresis

Calcium entry blockers (CEBs), especially dihydropyridines such as felodipine, are powerful vasodilating drugs useful for the treatment of hypertension. These drugs have short-term diuretic and natriuretic effects, which may contribute to their antihypertensive action. Clearance studies in humans and some micropuncture studies in animals have indicated that CEBs decrease proximal tubular sodium reabsorption. However, the mechanisms responsible for CEB-mediated natriuresis remain unknown. Since selective administration of a CEB into the renal artery stimulates natriuresis, an interaction with intrarenal natriuretic systems such as the dopaminergic system could be involved.

We and others have observed that the increased sodium excretion during calcium entry blockade is not accompanied by a parallel increase of potassium excretion. This is rather surprising in view of the aforementioned CEB-mediated decrease of proximal tubular sodium reabsorption. We have previously demonstrated that simultaneous administration of exogenous aldosterone and felodipine was followed by a large increase of kaliuresis. Therefore, the attenuation of potassium excretion during calcium entry blockade might be explained by the well-known CEB-mediated inhibition of aldosterone release.

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We and others have observed that the increased sodium excretion during calcium entry blockade is not accompanied by a parallel increase of potassium excretion. This is rather surprising in view of the aforementioned CEB-mediated decrease of proximal tubular sodium reabsorption. We have previously demonstrated that simultaneous administration of exogenous aldosterone and felodipine was followed by a large increase of kaliuresis. Therefore, the attenuation of potassium excretion during calcium entry blockade might be explained by the well-known CEB-mediated inhibition of aldosterone release.

Dopamine exerts its biological effects through occupation of the type 1 and type 2 receptor subtypes (DA1 and DA2). Stimulation of DA1 receptors induces renal vasoconstriction and natriuresis, whereas activation of the DA2 receptors can promote sodium excretion directly by inhibition of norepinephrine and aldosterone release. DA2 receptor blockade attenuated the natriuretic effect of calcium entry blockade in spontaneously hypertensive rats, and preferential DA2 receptor blockade with metoclopramide prevented the natriuretic effect of a low dose of a CEB in hypertensive humans. Therefore, both DA1 and DA2 receptor stimulation should be considered as possible mechanisms mediating CEB-induced natriuresis.

Since selective DA1 receptor antagonists are not available for human studies, we also used metoclopramide to delineate the role of the dopaminergic system in the natriuretic effect of different felodipine doses. Metoclopramide also increases plasma aldosterone concentration (PAC) and thus enabled us to study the relation between CEB-induced natriuresis, endogenous aldosterone, and potassium excretion. In our previous study with exogenous aldosterone, this infusion resulted in a relatively high PAC above 2.5 nmol/L. We therefore questioned whether an increase of endogenous aldosterone within the normal physiological range would also increase potassium excretion during CEB-mediated natriuresis.

Methods

Subjects

Twelve healthy male volunteers participated in this study. All participants were free of medication. Ages ranged from 20 to 33 years (mean, 26); all had a blood pressure below 140/90 mm Hg (systolic, 102 to 140 mm Hg; diastolic, 66 to 140 mm Hg). Ages ranged from 20 to 33 years (mean, 26); all had a blood pressure below 140/90 mm Hg (systolic, 102 to 140 mm Hg; diastolic, 66 to
were measured by standard semiautomated techniques, and levels for the last 90 minutes (therapeutic dose). To reach
this, 0.10 µg/kg per minute of felodipine (Plendil) was infused through a separate intravenous cannula into the upper arm at
an infusion rate of 20 mL/h for the first 30 minutes (1 mg metoclopramide/mL) or 5% dextrose alone was infused
to a standard body surface area of 1.73 m². Fractional proximal sodium reabsorption (FPRNa) and fractional distal sodium reab-
sorption (FDRNa) were calculated by the lithium clearance method:25 FPRNa = 1 – ClNa/GFR and FDRNa = 1 – ClNa/ClNa.

Statistical Analysis
For baseline levels, means of the first two urine collection periods were calculated. The fourth urine collection period, measured just before felodipine or solvent was started, was used as pretreatment level. For the low and therapeutic felodipine doses, mean values of the last two urine collections of each 90-minute period were calculated; ie, mean values of the sixth and seventh and mean values of the ninth and tenth clearance periods were used, respectively. The effects of metoclo-
pramide pretreatment were evaluated by comparing absolute changes from baseline level. The responses to felodipine infusions were evaluated by comparing absolute changes from pretreatment levels as measured just before felodipine or solvent was started. Infusion of felodipine alone was compared with placebo infusion and with felodipine during metoclopramide.

Statistics were performed with Statistical Analysis System (SAS) software, using the two-tailed Wilcoxon test for simple pairwise comparisons and repeated-measures ANOVA for comparison of baseline data. Probability values less than .05 were considered statistically significant. Results are presented as mean±SEM.

All 12 volunteers completed the three clearance experiments. The most common side effects were restlessness during or after metoclopramide infusion (6 of 12) and self-limiting headache during felodipine infusion (4 of 12 compared with 2 of 12 with solvent). One volunteer complained of drowsiness during felodipine infusion.

Baseline Data
Body weights and 24-hour urinary water, sodium, and potassium excretions were comparable before the three clearance experiments (Table 1). Baseline MAP was slightly lower before metoclopramide infusion (Fig 1). All other baseline levels of systemic and renal hemody-
namics as well as baseline electrolyte excretions did not differ among the three experimental periods (Figs 1, 2, and 4; Table 2).

Systemic and Renal Hemodynamics
Infusion of the low felodipine dose decreased MAP from a pretreatment level of 89±3 to 86±2 mm Hg (Fig 1) and increased heart rate from 55±2 to 60±2 beats per minute (bpm) (both P<.05 compared with changes with solvent). The therapeutic felodipine dose increased heart rate further to 65±± bpm (P<.01), whereas the change in MAP no longer differed from the change with
solvent ($P>.10$, Fig 1). Metoclopramide pretreatment did not change blood pressure or heart rate and did not influence the felodipine-mediated blood pressure changes. During simultaneous infusion of metoclopramide and the therapeutic felodipine dose, the rise of heart rate was more pronounced than with felodipine alone (+16±3 and +10±1 bpm, respectively, $P<.05$).

Felodipine infusion alone induced dose-related increases of RPF (Fig 1) and decreases of FF ($0.023±0.004$ at low dose and $0.037±0.005$ at therapeutic dose; both $P<.05$ compared with solvent). Felodipine did not change GFR (Fig 1). Metoclopramide infusion had no major effect on renal hemodynamic parameters. Felodipine infusion induced the same renal vasoconstriction during metoclopramide as during dextrose, with comparable increases of RPF (low dose, $+68±14$ and $+74±16$ mL/min per 1.73 m$^2$; therapeutic dose, $+128±15$ and $+152±27$ mL/min per 1.73 m$^2$, $P>.10$ for both doses; Fig 1).

**Diuresis and Natriuresis**

Felodipine infusion alone had distinct and dose-dependent diuretic and natriuretic effects, with parallel changes of chloride excretion (Fig 2 and Table 2). Metoclopramide induced a slight decrease of urinary flow rate and a minor decrease of sodium excretion that was only significant compared with dextrose preceding felodipine (Fig 2 and Table 2). During ongoing metoclopramide infusion, felodipine still induced pronounced increases of natriuresis and diuresis, which were comparable to the responses with felodipine alone (Fig 3). Only the increase of UNaV induced by the low felodipine dose tended to be attenuated by metoclopramide ($+136±29$ compared with $+171±26$ μmol/min with felodipine alone, $P=.06$).

Both felodipine doses significantly increased $C_{Li}$ (Table 2) and decreased calculated $FPR_{Na}$ (data not

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**TABLE 1. Steady-State Data Before Clearance Studies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dext+Solv</th>
<th>Dext+Felo</th>
<th>Meto+Felo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>73.1±1.5</td>
<td>72.9±1.6</td>
<td>72.9±1.6</td>
</tr>
<tr>
<td>Urine volume, mL/24 h</td>
<td>1315±83</td>
<td>1488±104</td>
<td>1424±134</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>135±10</td>
<td>139±9</td>
<td>156±20</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>75±5</td>
<td>77±7</td>
<td>80±8</td>
</tr>
</tbody>
</table>

Dext indicates dextrose; Solv, solvent; Felo, felodipine; and Meto, metoclopramide. Dextrose and solvent were both used as placebo. Values are mean±SEM.

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Fig 1. Line graphs show systemic and renal hemodynamics during drug and placebo infusions. Infusion schedule is indicated by bars at the bottom. Open circles indicate dextrose followed by solvent; open squares, dextrose followed by felodipine; and closed squares, metoclopramide followed by felodipine. Low-F and ther-F indicate low and therapeutic felodipine doses. Absolute changes from baseline level were compared to evaluate pretreatment effect and absolute changes from pretreatment level to evaluate responses to felodipine infusion. $*P<.05$ for comparison of metoclopramide+felodipine and dextrose+felodipine; $4P<.05$, $6P<.01$ for comparison of dextrose+felodipine and dextrose+solvent.

Fig 2. Line graphs show diuresis and natriuresis during drug and placebo infusions. Infusion schedule is indicated by bars at the bottom. Open circles indicate dextrose followed by solvent; open squares, dextrose followed by felodipine; and closed squares, metoclopramide followed by felodipine. Low-F and ther-F indicate low and therapeutic felodipine doses. Absolute changes from baseline level were compared to evaluate pretreatment effect and absolute changes from pretreatment level to evaluate responses to felodipine infusion. $*P<.05$, $3P<.01$ for comparison of metoclopramide+felodipine and dextrose+felodipine; $6P<.01$ for comparison of dextrose+felodipine and dextrose+solvent.
TABLE 2. Electrolyte Excretions Before and During Drug and Placebo Infusions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period</th>
<th>Baseline</th>
<th>Pretreatment</th>
<th>Low-F</th>
<th>Ther-F</th>
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</thead>
<tbody>
<tr>
<td>U_{Na}V, μmol/min</td>
<td>Dext+Solv</td>
<td>155±20</td>
<td>134±14</td>
<td>167±20$</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>142±17</td>
<td>141±21</td>
<td>312±37</td>
<td>537±65</td>
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<tr>
<td></td>
<td>Meto+Felo</td>
<td>171±27</td>
<td>139±22$*$</td>
<td>275±38</td>
<td>489±81</td>
</tr>
<tr>
<td>U_{K}V, μmol/min</td>
<td>Dext+Solv</td>
<td>91±9</td>
<td>70±4$†$</td>
<td>58±4$‡$</td>
<td>50±4$‡$</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>70±8</td>
<td>63±7</td>
<td>88±12$§$</td>
<td>70±7</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>84±11</td>
<td>66±9</td>
<td>100±10$‡$</td>
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</tr>
<tr>
<td>U_{Cl}V, μmol/min</td>
<td>Dext+Solv</td>
<td>129±18</td>
<td>100±11</td>
<td>110±16$‡$</td>
<td>423±54</td>
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<td></td>
<td>Dext+Felo</td>
<td>115±16</td>
<td>98±14</td>
<td>226±24</td>
<td>430±71</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>143±23</td>
<td>114±16</td>
<td>239±35</td>
<td>239±35</td>
</tr>
<tr>
<td>Cl_{Li}, mL/min</td>
<td>Dext+Solv</td>
<td>32±2</td>
<td>31±2</td>
<td>31±2$‡$</td>
<td>31±2$‡$</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>31±2</td>
<td>32±1</td>
<td>38±2</td>
<td>43±2</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>29±2</td>
<td>27±2$†$</td>
<td>36±3</td>
<td>44±4</td>
</tr>
</tbody>
</table>

$\ast P<.01$, $†P<.05$ compared with dext+felo for pretreatment effect, comparison of absolute changes from baseline level.

$‡P<.01$, $§P<.05$ compared with dext+felo for responses to felodipine infusion, absolute changes from pretreatment level.

Low-F indicates low felodipine dose; Ther-F, therapeutic felodipine dose; U_{Na}V, U_{K}V, U_{Cl}V, urinary excretions of sodium, potassium, and chloride; Cl_{Li}, lithium clearance; and definitions as in Table 1. Baseline values were comparable.

shown) and FDR_{Na} (Fig 4). Metoclopramide did not affect the large felodipine-mediated increase of Cl_{Li} and decrease of FPR_{Na}. Only the decrease of FDR_{Na} induced by the low felodipine dose was blunted by metoclopramide (Fig 3).

Kaliuresis

As observed in our other studies,$^6-13$ potassium excretion steadily decreased with time on placebo days (Fig 4 and Table 2), which is probably related to the absence of oral potassium intake and the declining PAC in our supine subjects. In contrast, no such decrease of kaliure-

![Kaliuresis Graph](image-url)
but insignificantly attenuated by metoclopramide. Thus, with felodipine alone (Fig 4). However, metoclopramide induced a large rise of PAC from 0.17±0.03 to 0.66±0.13 to 0.46±0.14 nmol/L; P<.05 (Fig 4).

**Hormones and Plasma Drug Levels**

PRA gradually decreased during combined placebo infusion from a baseline level of 0.66±0.13 to 0.46±0.14 nmol/L per hour at the end of the experiment. On the other two experimental days, similar decreases of PRA were observed without any significant influence of metoclopramide or of either felodipine dose. PRA decreased by 0.20±0.08 nmol/L per hour with felodipine alone and by 0.07±0.11 nmol/L per hour with felodipine during metoclopramide.

PAC also steadily decreased on placebo days and with felodipine alone (Fig 4). However, metoclopramide induced a large rise of PAC from 0.17±0.03 to 0.66±0.14 nmol/L (P<.01 compared with dextrose), and PAC remained clearly higher during subsequent felodipine infusion than during felodipine alone (low dose, 0.47±0.10 versus 0.12±0.02 nmol/L, P<.001; therapeutic dose, 0.32±0.08 versus 0.13±0.04 nmol/L, P=.02; Fig 4).

Infusion of the low felodipine dose led to stable, subtherapeutic plasma levels of approximately 4 nmol/L. Increasing the dose more than doubled the drug levels to a therapeutic level of 9 nmol/L (Fig 5). Felodipine plasma levels were slightly but significantly higher during concomitant metoclopramide infusion (low dose, 4.8±0.3 versus 3.9±0.3 nmol/L with felodipine alone; therapeutic dose, 9.3±0.4 versus 9.0±0.3 nmol/L; P<.05 for area under the curve).

**Discussion**

In the present study in healthy volunteers, the dopamine antagonist metoclopramide had no significant influence on the natriuretic and diuretic effects of either the low or therapeutic dose of felodipine. Only the natriuretic effect of the low felodipine dose was slightly but insignificantly attenuated by metoclopramide. Thus, our data suggest that the natriuretic and diuretic effects of calcium entry blockade cannot be explained by an interaction with the part of the intrarenal dopaminergic system that is blocked by metoclopramide.

Metoclopramide exhibits a preferential DA2 receptor selectivity, 28,29; however, at high doses also tubular DA1 receptors are blocked. 31 Thus, the question arises of whether the dose in our study was high enough to block the tubular DA1 receptors, which directly mediate dopamine-induced natriuresis. 8,16,17 In two studies in healthy volunteers, the same metoclopramide infusion schedule as used in the present study inhibited the natriuretic responses to a low dose of dopamine33 and to the selective DA1 agonist fenoldopam. 34 However, in another study, an infusion of approximately two thirds of our metoclopramide dose did not affect dopamine-mediated natriuresis in salt-loaded healthy subjects. 35 These data might suggest that our metoclopramide dose was just high enough to block DA1 receptor–mediated natriuresis. However, the inhibitory effect of metoclopramide on sodium excretion in the aforementioned two studies33,34 might alternatively be ascribed to the observed and well-known metoclopramide-mediated release of PAC. Therefore, our results allow us to conclude only that DA2 receptors are not involved in the natriuretic effect of felodipine. These data thus confirm earlier studies in hypertensive patients, in whom the selective DA2 receptor antagonist domperidone did not influence the natriuretic effect of the CEB nicardipine. 36 Only the use of a potent DA1 receptor antagonist would have allowed us to draw definitive conclusions on the role of DA1 receptors in the natriuretic response to calcium entry blockade, but unfortunately such compounds are not available for human studies. Of note, the selective DA1 antagonist SCH 23990 prevented the natriuretic effect of nitrendipine and diltiazem in spontaneously hypertensive rats. 19 However, it is difficult to translate these data to the human situation because very high drug doses were used, and consequently very large blood pressure changes were observed.

Our results do not exclude the possibility that metoclopramide slightly attenuates the natriuretic effect of low doses of CEBs. Although the effects of metoclopramide on felodipine-induced natriuresis failed to reach statistical significance, sodium excretion tended to be lower. However, plasma felodipine levels were higher during concomitant metoclopramide infusion, possibly because of a decreased metabolic clearance of felodipine. As the natriuretic effects of CEBs appear to be dose dependent, 37 one might have expected higher sodium excretion rates in this period with higher felodipine levels. Our data are thus in line with observations in hypertensive patients, in whom metoclopramide largely prevented the natriuresis of a very low dose of nicardipine but did not affect the natriuretic action of a therapeutic dose. 20 Taken together, these data might suggest a role, albeit limited, for the metoclopramide blockable part of the dopaminergic system in CEB-induced natriuresis. However, the attenuation of the natriuretic effect of low doses of CEBs could easily be explained by the metoclopramide-induced large increase of PAC, which might have attenuated the natriuresis with felodipine comparable to the attenuation of natriuresis in our study with exogenous aldosterone and felodipine. 13 This possibility is further supported by the
results of the present study in which metoclopramide attenuated the felodipine-mediated decrease of distal and not of proximal tubular sodium reabsorption.

In the setting of elevated PAC during metoclopramide infusion, felodipine induced an immediate increase of potassium excretion. This observation is noteworthy because we and others have observed that the natriuresis of calcium entry blockade is usually not accompanied by an increase of kaliuresis. This absence of kaliuresis is surprising in view of the fact that clearances studies in humans and some microencapsulation studies in animals have indicated that CEBs decrease proximal tubular sodium reabsorption. Such a decrease in proximal sodium reabsorption and the subsequent increase of distal tubular sodium and fluid load should normally enhance potassium excretion, as is observed with diuretics such as furosemide. Thus, it seems likely that CEBs also act at a distal tubular site. In this respect, it is of interest that dihydropyridine CEBs can induce a rise of PRA without a parallel increase of PAC, possibly because of direct inhibition of aldosterone release by adrenal glomerulosa cells. We suggest that this inhibition of aldosterone release is essential for the dissociation between the natriuretic and kaliuretic effects of CEBs. In a previous study, we demonstrated that adding exogenous aldosterone to a felodipine infusion resulted in a major increase of potassium excretion that was more pronounced than with aldosterone alone. However, definite conclusions could not be drawn because PAC levels were relatively high (>2.5 mmol/L). Our present findings now confirm that elevated endogenous aldosterone levels within the physiological range, as induced by metoclopramide, also enabled felodipine to induce kaliuresis. In this respect, it should be noted that our study lacked a control period with metoclopramide alone. However, it is unlikely that metoclopramide administration per se is the cause of the increased potassium excretion, because other researchers have not observed such kaliuretic effects of metoclopramide.

In conclusion, dopaminergic receptor blockade with metoclopramide does not prevent the natriuretic effect of low and therapeutic felodipine doses, thereby indicating that the metoclopramide blockable part of the dopaminergic system does not play a major role in the natriuretic action of CEBs. In contrast to felodipine alone, simultaneous infusion of metoclopramide and felodipine led to a marked kaliuresis as a consequence of the metoclopramide-mediated rise of aldosterone. This confirms earlier findings with exogenous aldosterone and indicates that CEBs will induce kaliuresis if sufficient amounts of aldosterone are available. The inhibitory effect of CEBs on aldosterone release thus prevents urinary potassium losses despite an increase of natriuresis and diuresis.

Acknowledgments

This work was supported by a grant (C86.617) from the Dutch Kidney Foundation and by Astra Pharmaceuticals BV, Rijswijk, Netherlands. Felodipine was supplied by AB Astra Hässle, Möln达尔, Sweden, where felodipine plasma levels also were determined. We thank Marijke Rodermund and Gertie van Casteren for their skillful technical assistance. We also would like to acknowledge the staff and coworkers of the laboratories of Clinical Chemistry (head: Dr Hans L. Willems) and the department of Experimental and Chemical Endocrinology (head: Prof Dr Theo J. Benraad) for the many laboratory determinations.

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Hypertension. 1994;24:633-639
doi: 10.1161/01.HYP.24.5.633

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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