Domperidone, a DA₂-specific dopamine antagonist, has no effect on the renal or haemodynamic response to atrial natriuretic peptide in man

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SUMMARY

1. Animal experiments have suggested that the renal effects of atrial natriuretic peptide (ANP) are dependent on dopaminergic activation, predominantly of the DA₁-receptor. In man, there is evidence of dependence on the DA₂-receptor for the natriuresis produced by central blood volume expansion.

2. Six normal volunteers underwent infusions of α-human ANP preceded by domperidone (a DA₂-antagonist) or placebo. Eight volunteers underwent a 3 h period of 10° head-down tilt also preceded by domperidone or placebo.

3. Both the ANP infusion and head-down tilt produced a significant diuresis and natriuresis, neither of which was antagonized by the presence of domperidone.

4. The ANP infusion significantly reduced diastolic blood pressure and produced significant increases in the Doppler-measured aortic blood velocity variables of peak velocity and maximal acceleration. Domperidone had an independent effect of increasing blood pressure but did not appear to have a specific interaction with the haemodynamic effects of ANP.

5. Head-down tilt reduced mean arterial pressure and heart rate and increased maximal acceleration. Again, an independent effect of domperidone was seen on blood pressure. Heart rate and maximal acceleration showed similar changes in the presence of domperidone.

6. Domperidone does not antagonize the renal or haemodynamic effects of ANP and if dopaminergic activation is necessary for the renal action of ANP it is unlikely to be mediated by the DA₂-receptor.

Key words: atrial natriuretic peptide, dopamine, domperidone.

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Abbreviations: ANP, atrial natriuretic peptide; CL₁, clearance of lithium; Clₙa, clearance of sodium; α-hANP, α-human atrial natriuretic peptide; MA, maximum acceleration; MD, minute distance; PkV, peak velocity; SD, stroke distance.

INTRODUCTION

Increases in central blood volume, i.e. a redistribution of blood volume to the intrathoracic and intra-abdominal vessels, will cause atrial stretch, a diuresis and a natriuresis. This has been conclusively demonstrated with water immersion [1], lower-body positive pressure [2] and head-down tilt [3]. It has been suggested that this response is predominantly due to the release of atrial peptides which have certainly been shown to be increased under these conditions [3, 4].

Peripheral dopamine (3,4-dihydroxyphenethylamine) receptors can be divided into two types, DA₁ and DA₂, which seem to correspond to the D₁- and D₂-receptors in the central nervous system. The DA₁-receptor can best be demonstrated in vascular smooth muscle. When activated it causes the release of adenosine 3',5'-cyclic monophosphate and subsequent vasodilatation. The DA₂-receptor is found on presynaptic adrenergic nerve terminals and when activated inhibits the releases of noradrenaline. It is probably the distribution of these two receptors types that determines the differential effects of dopamine on the renal, mesenteric and systemic circulations.

Two studies in man have demonstrated an inhibition of the natriuresis caused by increased central blood volume by the DA₂-specific dopamine antagonist domperidone [2, 5]. Animal studies have suggested that the natriuretic response to atrial peptides may be dependent on dopaminergic activation in that it can be blocked by dopamine antagonists. Most of the evidence to date, however, suggests that this is specific to blockade of the DA₁-receptor [6–9]. More recently, Freestone et al. [10] have
demonstrated that blockade of the DA1-receptor in man has no effect on the renal response to atrial natriuretic peptide (ANP).

Atrial peptides seem to have their effects by activation of specific receptors leading to activation of particulate guanylate cyclase and guanosine 3',5'-cyclic monophosphate as a second messenger [11, 12]. The proposed role of dopamine in this scheme is therefore unclear unless it can modulate theresponsiveness of the ANP receptor or a degree of dopaminergic tone is necessary for the activated guanosine 3',5'-cyclic monophosphate to be effective. There is no evidence to suggest that dopamine antagonists are antinatriuretic when given alone although inhibition of intrarenal dopamine production from l-dopa with the dopa decarboxylase inhibitor carbipoda (5-α-hydrazino-3,4-dihydroxy-α-methyl benzene propanoic acid monohydrate) has been shown to reduce sodium excretion in norman man [13].

This study was designed to investigate the effect of blockade of the DA1-receptor on the renal response to both exogenous atrial peptide and to central blood volume expansion with head-down tilt. In the case of head-down tilt the lithium clearance \( (C_{Li}) \) technique [14] was also used to assess differential effects on the proximal and distal nephron.

**METHODS**

The study was designed in two parts. In the first part, six normal volunteers received placebo and ANP infusions, the latter after oral pretreatment with 60 mg of domperidone (Motilium; Janssen Pharmaceuticals) or a placebo in a double-blind cross-over experiment. In the second part, eight volunteers spent 3 h with head-down tilt of 10° after pretreatment with 60 mg of domperidone or placebo orally, again in a double-blind cross-over study. All subjects were maintained on a diet giving a sodium intake of 120 mmol/day for a minimum of 4 days before each study. Alcohol and caffeine were banned for 24 h before each study. The subjects were fasted on the study days, except for oral water loading with 500 ml of tap water on rising and a further 250 ml on arrival in the laboratory at 08.30 hours. Written informed consent was obtained from each subject and approval for the study was given by the District Medical Ethical Committee.

**Part 1**

Each subject attended twice and sat upright for the duration of the experiment. For the first 20 min on each occasion they were given a placebo infusion (saline, 0.9 g NaCl/100 ml, at a rate of 1 ml/min) and urine collections were made over the subsequent 120 min for measurement of volume, sodium and creatinine. Calculations were made of creatinine clearance, sodium excretion rate and fractional sodium excretion. Haemodynamic measurements were made, in duplicate, before the infusion and at 15 min from the start of infusion. These consisted of heart rate, arterial blood pressure and Doppler measurement of aortic blood flow (Exerdop; Quinton, Seattle, WA, U.S.A.). The Doppler parameters measured were stroke distance (SD) which is proportional to stroke volume, peak velocity (Pv) and maximal acceleration (MA) [15]. Calculation was made from the Doppler variables of minute distance (MD; SD x heart rate), a Doppler index of cardiac output.

Subjects were then given domperidone or placebo in randomized order and after a further 30 min they received a 20 min infusion of α-human ANP (α-hANP; Peninsula Laboratories) at a rate of 5 μg/min which will produce a tenfold increase in plasma levels [16]. The α-hANP was diluted in 20 ml of saline, passed through a 0.2 μm filter and given at a rate of 1 ml/min. Urinary and haemodynamic measurements were made as with the placebo infusion. Haemodynamic measurements were also made in duplicate before and 30 min after the domperidone.

**Part 2**

Each volunteer attended twice having taken 500 mg of lithium carbonate (Camcolit, Norgine Ltd) the previous evening and after a 60 min control period sitting upright spent the next 180 min lying with 10° head-down tilt. They received domperidone or placebo in a double-blind randomized order 30 min into the control period. Haemodynamic measurements and blood samples for plasma ANP were made before the domperidone/placebo and after 30 min, and then hourly during the period of head-down tilt. Blood was taken for lithium assay at hourly intervals. Urine was collected hourly for calculation of flow rate, sodium excretion rate and clearance \( (C_{Na}) \), creatinine clearance and \( C_{Li} \).

Blood samples for ANP assay were collected into chilled tubes containing ethylenediaminetetra-acetate and aprotinin (Trasylool, Bayer) and immediately centrifuged. The plasma was frozen on dry ice and stored at −20°C until assayed. ANP assay was performed after extraction through a Sep-Pak C18 cartridge as described previously [16]. Plasma sodium was measured by an ion-selective electrode, plasma and urinary creatinine by the Jaffe method, urinary sodium by flame photometry, and plasma and urinary lithium by atomic absorption spectrometry.

**Statistics**

Results are expressed as means ± SEM. Two-way analysis of variance ('Statworks' software for the Apple Macintosh computer) was used to examine the urine data and when significant paired Student's t-tests were used to localize the differences. Paired Student's t-tests were also used to compare haemodynamic variables before and during ANP and before and after domperidone.

**RESULTS**

**Part 1**

ANP increased urine flow from 7.5 ± 0.7 to 11.5 ± 0.3 ml/min (P < 0.005). With the addition of domperidone, this increase was not significantly different (6.6 ± 1.2 to
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10.8 ± 0.7 ml/min (Fig. 1). Similarly, ANP alone increased sodium excretion from 87 ± 19 to 200 ± 43 μmol/min (P < 0.001), and with the addition of domperidone the increase was not significantly different (111 ± 15 to 230 ± 36 μmol/min) (Fig. 1). Creatinine clearance was not significantly changed by ANP (133 ± 2 ml/min before, 139 ± 12 after) or domperidone (131 ± 2 ml/min before, 123 ± 3 after). Fractional sodium excretion increased with ANP alone from 0.46 ± 0.07 to 1.06 ± 0.22% and with ANP plus domperidone from 0.63 ± 0.09 to 1.37 ± 0.24%. Again, this was a significant effect of ANP (P < 0.01) which was not affected by the addition of domperidone.

Domperidone had an independent effect of increasing mean arterial pressure from 92 (12.1) ± 3 (0.4) to 96 (12.6) ± 2 (0.3) mmHg (kPa) (P < 0.001). No significant change was seen after the placebo tablets. Domperidone had no effect on heart rate or the Doppler variables of SD, PkV, MA or MD.

ANP did not produce significant changes in mean arterial blood pressure [93 (12.2) ± 2 (0.3) mmHg (kPa) before ANP, 90 (11.8) ± 3 (0.4) mmHg (kPa) during ANP] (Table 1). In the presence of domperidone a similar nonsignificant tendency was seen [96 (12.6) ± 2 (0.3) before ANP, 93 (12.2) ± 2 (0.3) mmHg (kPa) during ANP]. Significant falls did, however, occur in diastolic blood pressure [82 (10.8) ± 3 (0.4) dropping to 77 (10.1) ± 3 (0.4) with ANP alone, P < 0.03, and 84 (11.1) ± 3 (0.4) to 80 (10.5) ± 3 (0.4) mmHg (kPa) in the presence of domperidone, P < 0.03] (Table 1). ANP had no effect on heart rate (60 ± 2 before and 61 ± 2 during ANP) or MD (669 ± 23 before and 665 ± 25 cm/min during ANP) (Table 1).

Part 2

Head-down tilt increased urinary flow progressively from a control value of 6.6 ± 1.2 to 9.5 ± 0.7 ml/min by the third hour (P < 0.02) (Fig. 2). In the presence of dom-

![Graph](image-url)

**Fig. 1.** Effect of ANP and placebo infusions on urinary flow and sodium excretion in the presence of domperidone (■) and placebo (○) in six normal volunteers. Results are means ± SEM. Analysis of variance for urinary flow: effect of ANP, P < 0.005; effect of domperidone on ANP response, not significant. Analysis of variance for sodium excretion: effect of ANP, P < 0.001; effect of domperidone on ANP response, not significant.

10.8 ± 0.7 ml/min (Fig. 1). Similarly, ANP alone increased sodium excretion from 87 ± 19 to 200 ± 43 μmol/min (P < 0.001), and with the addition of domperidone the increase was not significantly different (111 ± 15 to 230 ± 36 μmol/min) (Fig. 1). Creatinine clearance was not significantly changed by ANP (133 ± 2 ml/min before, 139 ± 12 after) or domperidone (131 ± 2 ml/min before, 123 ± 3 after). Fractional sodium excretion increased with ANP alone from 0.46 ± 0.07 to 1.06 ± 0.22% and with ANP plus domperidone from 0.63 ± 0.09 to 1.37 ± 0.24%. Again, this was a significant effect of ANP (P < 0.01) which was not affected by the addition of domperidone.

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**Table 1.** Haemodynamic effects of ANP, domperidone and ANP plus domperidone in six normal volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before ANP</th>
<th>During ANP</th>
<th>Before ANP</th>
<th>After domperidone before ANP</th>
<th>After domperidone and ANP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>93 ± 2</td>
<td>90 ± 3</td>
<td>92 ± 3</td>
<td>96 ± 2</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116 ± 2</td>
<td>115 ± 4</td>
<td>115 ± 2</td>
<td>119 ± 2</td>
<td>120 ± 3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82 ± 3</td>
<td>77 ± 3</td>
<td>80 ± 3</td>
<td>84 ± 3</td>
<td>80 ± 3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>60 ± 1.5</td>
<td>61 ± 2.3</td>
<td>57 ± 2.0</td>
<td>61 ± 2.4</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>SD (cm)</td>
<td>11.3 ± 0.6</td>
<td>11.0 ± 0.7</td>
<td>12.4 ± 0.9</td>
<td>12.0 ± 1.0</td>
<td>11.1 ± 0.4</td>
</tr>
<tr>
<td>MD (cm/min)</td>
<td>669 ± 23</td>
<td>665 ± 25</td>
<td>716 ± 66</td>
<td>732 ± 73</td>
<td>651 ± 27</td>
</tr>
<tr>
<td>PkV (m/s)</td>
<td>0.77 ± 0.03</td>
<td>0.85 ± 0.05</td>
<td>0.78 ± 0.01</td>
<td>0.79 ± 0.03</td>
<td>0.85 ± 0.03</td>
</tr>
<tr>
<td>MA (ms⁻²)</td>
<td>16.7 ± 0.6</td>
<td>19.5 ± 0.9</td>
<td>16.8 ± 0.7</td>
<td>16.8 ± 1.1</td>
<td>19.8 ± 0.8</td>
</tr>
</tbody>
</table>
Effect of head-down tilt on urinary volume and sodium excretion in the presence of domperidone and placebo in eight volunteers. Results are means ± SEM.

Analysis of variance for urine flow: effect of tilt, \( P < 0.02 \); effect of domperidone on tilt response, not significant. Analysis of variance for sodium excretion: effect of tilt, \( P < 0.005 \); effect of domperidone on tilt response, not significant.

Plasma ANP increased significantly with head-down tilt from 3.41 ± 0.35 pg/ml to a maximum of 6.06 ± 0.88 pg/ml (\( P < 0.002 \)) which was not affected by the presence of domperidone [2, 5], a DA\(_2\)-specific antagonist [17, 18], whilst the renal effects of ANP were not blocked by \( \alpha \)-sulpride, a DA\(_1\)-specific antagonist [10].

This study demonstrates that antagonism of the DA\(_2\)-receptor in man does not inhibit the renal response to
Table 2. Haemodynamic effects of head-down tilt in the presence of domperidone and placebo in eight normal volunteers

Results are means ± SEM. Abbreviations: MAP, mean arterial pressure; HR, heart rate; NS, not significant. SD, MD, PkV and MA are data determined from Doppler-measured ascending aortic blood velocity. Statistical significance: *P<0.05, **P<0.005.

<table>
<thead>
<tr>
<th></th>
<th>Erect Head-down</th>
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<th>Analysis of variance</th>
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<tbody>
<tr>
<td></td>
<td>60 min</td>
<td>120 min</td>
<td>180 min</td>
<td></td>
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<tr>
<td>MAP (mmHg)</td>
<td></td>
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</tr>
<tr>
<td>Placebo</td>
<td>91.9 ± 1.5</td>
<td>86.2 ± 2.4</td>
<td>87.6 ± 2.4</td>
<td>0.032</td>
</tr>
<tr>
<td>Domperidone</td>
<td>89.6 ± 1.7</td>
<td>88.6 ± 2.8</td>
<td>85.9 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
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<tr>
<td>Placebo</td>
<td>61.7 ± 1.4</td>
<td>56.3 ± 1.2</td>
<td>57.0 ± 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Domperidone</td>
<td>61.3 ± 1.5</td>
<td>56.8 ± 2.1</td>
<td>59.3 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>SD (cm)</td>
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<tr>
<td>Placebo</td>
<td>11.5 ± 0.9</td>
<td>13.3 ± 1.4</td>
<td>14.4 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Domperidone</td>
<td>12.5 ± 0.9</td>
<td>12.3 ± 1.2</td>
<td>13.1 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>MD (cm/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>709 ± 42</td>
<td>696 ± 56</td>
<td>731 ± 60</td>
<td>NS</td>
</tr>
<tr>
<td>Domperidone</td>
<td>728 ± 44</td>
<td>710 ± 66</td>
<td>760 ± 90</td>
<td>NS</td>
</tr>
<tr>
<td>PkV (m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.77 ± 0.04</td>
<td>0.84 ± 0.03</td>
<td>0.84 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Domperidone</td>
<td>0.80 ± 0.04</td>
<td>0.81 ± 0.04</td>
<td>0.89 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>MA (m s⁻¹ s⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>16.3 ± 0.9</td>
<td>18.1 ± 0.7</td>
<td>19.0 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Domperidone</td>
<td>16.5 ± 1.4</td>
<td>18.0 ± 1.4</td>
<td>18.4 ± 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 4. Effect of head-down tilt on plasma ANP in the presence of domperidone (●) and placebo (□) in eight normal volunteers. Results are means ± SEM. Analysis of variance: for active domperidone (time 0–180 min), P<0.001; for placebo (time 0–180 min), P<0.002; for active domperidone vs placebo, not significant.

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Exogenous ANP or to head-down tilt with an increase in endogenous ANP. It is therefore in broad agreement with the animal data but not the human data.

There are now three studies in which domperidone has been given in combination with central blood volume expansion. Work from this laboratory in 1982 showed abolition of the natriuretic response to lower-body positive pressure by 40 mg of domperidone given intravenously [2]. Coruzzi et al. [5] demonstrated an attenuation, but not an abolition, of the natriuretic response to water immersion with domperidone (40 mg intravenously). In this study we have shown no effect of domperidone (60 mg orally) on the natriuresis of head-down tilt.

At first sight it would seem that the differences between the results of these studies might be due to differing doses of domperidone. The pharmacokinetics of domperidone in man have been examined [19] and from this we know that when 60 mg is given orally it has a bioavailability of around 14%, resulting in plasma levels in the region of 100 ng/ml falling to 10 ng/ml over the next 4 h, and also that 60 mg given orally is equivalent to about 8.4 mg given intravenously or 120 µg/kg given as an intravenous bolus.

The 40 mg given intravenously in the previous studies is equivalent to about 530 µg/kg. It has been shown in dogs that a dose of 5 µg/kg will achieve 75% DA₂-antagonism lasting for greater than 120 min but that doses of 5000 µg/kg have no effect on the DA₂-receptor [18]. If the dopamine receptors in man are equally sensitive and specific as in dogs, our study and the previous two human studies should each have achieved >75% antagonism of the DA₂-receptor with no effect on the DA₁-receptor. The apparent discrepancy may still result from differing doses if, at the higher dose, domperidone is having effects other than on dopamine receptors. These studies also differed in the methods by which they achieved central blood volume expansion. The current study uses head-down tilt whilst the previous studies used lower-body positive pressure and water immersion. It may be that additional natriuretic mechanisms are activated by the latter two techniques. Coruzzi et al. [5] noted a fall in plasma prolactin with water immersion which might suggest a role for central or circulating dopamine. We have found no such suppression of prolactin with head-down tilt (unpublished work).

Head-down tilt produced both a diuresis and natriuresis, although these effects seem to be independent. The
increase in volume occurs within the first hour, whereas sodium excretion is delayed until the second and third hours even though plasma ANP is increased immediately. This independence of volume and sodium may be due to additional inhibition of vasopressin release either directly via low pressure atrial receptors or via the effects of ANP on vasopressin release [16]. Although net sodium excretion was delayed for 60 min, sodium and water delivery to the distal nephron, as measured by $C_{\text{Na}}$ [14], increased within the first hour, suggesting that there was a transient compensatory increase in fractional sodium reabsorption in the distal nephron [Fig. 3]. In the second and third hours absolute sodium reabsorption in the distal nephron ($C_{\text{Na}} - C_{\text{Na}}$) remained elevated above baseline, but fractional sodium clearance ($C_{\text{Na}}/C_{\text{d}}$) was increased, resulting in a net natriuresis compared with the control period. We can only speculate as to the mechanisms of this biphasic response. Changes in periglomerular pressures or direct effects of ANP on the proximal nephron might account for the first phase, whilst aldosterone may have a role in the delayed distal nephron response. ANP has been shown to increase both sodium delivery to the distal nephron [20, 21] and to reduce sodium reabsorption from distal nephron fragments both in vitro [22] and in vivo [23] and may therefore contribute to either or both phases.

The haemodynamic effects of infused ANP were to reduce diastolic and mean blood pressure with little or no effect on the cardiac output or heart rate. This is in contrast with much of the animal work now published which suggests that the depressor effect of ANP is due to reduced cardiac output rather than changes in vascular resistance. It seems likely that this reduction in stroke volume is in turn due to reduced filling pressures, either due to reduction in plasma volume or increased venous compliance. The increases in PKV and MA seen in this study are evidence that there is no inhibitory effect on myocardial contractility [24] and it may be that cardiac output was maintained in this study by increased inotropy in the face of reduced filling pressures. Any difference between this response and that seen in animal experiments may relate to dosage variations or anaesthesia. The failure of the heart rate to increase has been well documented in other studies and put forward as evidence of a sympatholytic effect of ANP [25]. In the presence of domperidone the haemodynamic changes induced by ANP were similar, although domperidone had an independent effect of raising blood pressure. This might be expected from a drug that increases noradrenaline release from sympathetic nerve endings and has been previously documented by this laboratory to increase forearm vascular resistance when given systemically [26].

The haemodynamic effects of head-down tilt were a reduction in blood pressure and heart rate and increases in PKV and MA. The only response that altered in the presence of domperidone was the blood pressure, which is consistent with its independent effect.

In conclusion, domperidone does not inhibit the renal or haemodynamic responses to infused ANP or head-down tilt. If the renal response to ANP in man is dependent on dopaminergic activation, as suggested by animal experiments, this is unlikely to be mediated by the $DA_2$-receptor.

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REFERENCES


