The Effects of Different Doses of Dopamine and Domperidone on Increases of Plasma Norepinephrine Induced by Cold Pressor Test in Normal Man

Aloysius G. Lieverse*, Joop D. Lefrandt*, Armand R.J. Girbes*, Andries J. Smit* and Wepco D. Reitsma**

The effect of dopamine 1 and 3 µg/kg/min i.v., of dopamine 1 and 3 µg/kg/min i.v. combined with domperidone 30 mg per os and of placebo infusion on plasma norepinephrine concentration before and during sympathetic stimulation by a cold pressor test was investigated in 10 healthy volunteers (1 female, 9 males, mean age 28, range 19-41). Dopamine 1 µg/kg/min resulted in a blunting of the rise in plasma norepinephrine concentration during the cold pressor test, compared with placebo infusion. The addition of domperidone to dopamine 1 µg/kg/min abolished this effect. Plasma norepinephrine levels during dopamine 3 µg/kg/min infusion, both with and without domperidone, were not different from placebo, but significantly higher compared to dopamine 1 µg/kg/min infusion. Dopamine 1 and 3 µg/kg/min infusion, both with and without domperidone resulted in a blunted increase in blood pressure compared to placebo infusion. Dopamine 1 µg/kg/min infusion resulted in a lower systolic blood pressure during the cold pressor test compared to dopamine 3 µg/kg/min infusion. No significant changes in heart rate occurred during the cold pressor test comparing the different circumstances. We conclude that in healthy volunteers only dopamine 1 µg/kg/min, but not dopamine 3 µg/kg/min, blunts the increase in plasma norepinephrine concentration during a cold pressor test; this effect is abolished by pretreatment with domperidone. We hypothesize that dopamine 1 µg/kg/min does not affect plasma norepinephrine levels during exertion, because the DA-2 or µ-2 receptor mediated inhibitory effect of dopamine on norepinephrine release is counteracted by uptake-1 inhibition or enhanced synthesis and release of norepinephrine by dopamine. Although we had no evidence for hemodynamic differences between the exercise test with dopamine 1- and 3 µg/kg/min, respectively, the same limitation as for the study with ibopamine applies to the dopamine exercise protocol. Therefore, we attempted to separate effects mediated by the sympathetic nervous system from hemodynamic and other influences on venous norepinephrine levels by studying another model for sympathetic nervous system activation. When these same effects occur also in another model which activates the sympathetic nervous system and is associated with vasoconstriction instead of

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DA-2 receptors are situated prejunctionally on sympathetic nerve terminals. Stimulation of these receptors may result in an increase in norepinephrine release (1, 2). Iibopamine, an aselective dopamine agonist, blunts the rise of norepinephrine levels during exercise, a maneuver known to result in activation of the sympathetic nervous system (3). We hypothesized that this effect of ibopamine is due to DA-2 receptor stimulation. However, other mechanisms like a-2 receptor stimulation, changes in neuronal or extraneuronal reuptake or an increased clearance of norepinephrine due to an increased flow in the arm are possibly (also) involved. In another study we observed that dopamine 1 µg/kg/min did blunt the exercise induced increase in plasma norepinephrine levels. It might be that during infusion of dopamine 1 µg/kg/min the DA-2 dopaminergic inhibition of norepinephrine release blunts the increase in plasma norepinephrine during exercise. In contrast, dopamine 3 µg/kg/min did not change plasma norepinephrine levels at rest or during exercise. Dopamine 3 µg/kg/min combined with domperidone augmented the increase in norepinephrine levels during exercise. We hypothesized that dopamine 3 µg/kg/min does not affect plasma norepinephrine levels during exertion, because the DA-2 or µ-2 receptor mediated inhibitory effect of dopamine on norepinephrine release is counteracted by uptake-1 inhibition or enhanced synthesis and release of norepinephrine by dopamine. Although we had no evidence for hemodynamic differences between the exercise test with dopamine 1- and 3 µg/kg/min, respectively, the same limitation as for the study with ibopamine applies to the dopamine exercise protocol. Therefore, we attempted to separate effects mediated by the sympathetic nervous system from hemodynamic and other influences on venous norepinephrine levels by studying another model for sympathetic nervous system activation. When these same effects occur also in another model which activates the sympathetic nervous system and is associated with vasoconstriction instead of

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vasodilation, it is more probable that it is an effect on the sympathetic nervous system. In this study we investigate the effect of dopamine 1 and 3 \( \mu g/kg/min \) on increases in plasma norepinephrine levels during the cold pressor test, a test known to stimulate the sympathetic nervous system and to induce bilateral vasoconstriction in the forearm. Furthermore, the co-administration of domperidone, a DA-2 antagonist will be evaluated.

**Patients and Methods**

Ten healthy volunteers, 9 male, 1 female, were studied on three separate days with at least 3 days between each day of study using a single blind, cross over design. All studies were performed after fasting for at least 3 h. The three days of study (I, II, III) were planned in a randomly assigned sequence. Each day of study was randomly divided in study-period a and study-period b, with 50 min of rest in between.

On all days, 30 min before the start of the cold pressor test, the volunteers were given tablets and an antecubital vein was cannulated to enable infusion. On study-day I, placebo tablets and infusion of 5% glucose (as placebo) were used. During study-period IIa placebo tablets were given and infusion of dopamine 1 \( \mu g/kg/min \) in 5% glucose was administered, during study-period IIb placebo tablets were given and infusion of dopamine 3 \( \mu g/kg/min \) in 5% glucose was administered. During study-period IIIa domperidone 30 mg orally was given and infusion of dopamine 1 \( \mu g/kg/min \) in 5% glucose was administered, during study-period IIIb domperidone 30 mg orally was given and infusion of dopamine 3 \( \mu g/kg/min \) in 5% glucose was administered. The opposite arm was cannulated for frequent blood sampling and the Finapres-cuff (4) was applied to measure heart rate and blood pressure beat to beat non-invasively. Six blood samples were drawn. The outline of a study-period is given in Fig. 1. Before starting the infusion the first (t1) blood sample was drawn, after this the infusion was started and a subsequent period of 15 min of rest followed. After drawing the second (t2) blood sample, the cold pressor test was executed, lasting 3 min. The hand which was not used for blood sampling and heart rate and blood pressure measuring was put into a reservoir containing water with melting ice. For the timing of the remaining blood samples we refer to Fig. 1. After 50 min of rest, the second study-period with the alternative infusion-rate followed. All plasma samples were used to determine the plasma norepinephrine-concentration, with HPLC with electrochemical detection, after performing an extraction procedure, as described by Smedes et al. (5). The intra-assay coefficient of variance was 4.2% and the interassay coefficient of variance was 11%. All data, unless otherwise indicated, are shown as means ± standard error of the mean. In Fig. 2, the cumulative plasma norepinephrine during and just after the cold pressor test is shown (t3 + t4 + t5). Statistical analysis was performed using ANOVA. Differences were considered statistically significant at the 5% level. All volunteers gave their written informed consent before taking part in the study and the protocol was approved by the Medical Ethics Committee of the University Hospital of Groningen.

**Results**

All volunteers completed the study. No adverse effects were observed. The mean age was 28 (range 19-41) and the mean body mass index was 22.4 (range 18.9-24.8).

**Effects on Heart Rate and Blood Pressure**

(Table 1) Dopamine 1 and 3 \( \mu g/kg/min \) infusion, both with and without domperidone resulted in a blunted increase in blood pressure compared to placebo infusion. Dopamine 1 \( \mu g/kg/min \) infusion resulted in a lower systolic blood pressure during the cold pressor test compared to dopamine 3 \( \mu g/kg/min \) infusion. No significant changes in heart rate occurred during the cold pressor test comparing the different circumstances.

**Effects on Plasma Norepinephrine Concentration**

(Table 1 and Fig. 2) No differences in baseline plasma norepinephrine concentration were found between all study-periods. An increase in plasma norepinephrine concentration

**Fig. 1. Outline of a study-period. CA = plasma norepinephrine level, DMP = domperidone 30 mg orally.**

**Fig. 2. Cumulative plasma norepinephrine during and just after the cold pressor test (t3 + t4 + t5). *significant difference (p<0.05).**
occurred during the cold pressor test on all days. The maximal plasma norepinephrine concentration was reached at t5, 1.5 min after the cold pressor test.

Dopamine 1 µg/kg/min infusion resulted in a significantly blunted increase in plasma norepinephrine levels compared to placebo and dopamine 3 µg/kg/min infusion. The addition of domperidone to dopamine 1 µg/kg/min abolished the blunting compared to placebo but not to dopamine 3 µg/kg/min. Dopamine 3 µg/kg/min infusion, either with or without domperidone, had no effect on plasma norepinephrine levels compared with placebo.

Discussion

This study shows that infusion of dopamine 1 µg/kg/min blunts the increase in plasma norepinephrine levels during a cold pressor test, compared to either placebo infusion or dopamine 3 µg/kg/min infusion. In a previous study we observed that dopamine 1 µg/kg/min infusion was also associated with lower plasma norepinephrine levels during exercise compared to placebo. Presynaptic inhibition of norepinephrine release by DA-2 dopamine or α-2 adrenergic receptors may be responsible for this decrease in norepinephrine levels. One might argue that an increase in arm flow during exercise plus dopamine might also lead to such a fall in venous plasma norepinephrine levels. On the other hand, a cold pressor test will result in vasoconstriction and a fall in blood flow even in the contralateral arm (6). Thus a fall in norepinephrine levels with dopamine both during exercise, which gives rise to an increase in fore arm blood flow, and during a cold pressor test makes it unlikely that hemodynamic fall effects are responsible for either the increase in norepinephrine levels during both maneuvers or the inhibitory effects of dopamine. The difference in plasma norepinephrine levels between dopamine 1 and 3 µg/kg/min cannot be ascribed to more pronounced stimulation of DA-2 dopamine and α-2 adrenergic receptors during infusion of dopamine 3 µg/kg/min. On the contrary, this would be expected to result in lower plasma norepinephrine levels compared to dopamine 1 µg/kg/min infusion. Evidence exists that dopamine inhibits the re-uptake of norepinephrine in the synaptic cleft, also called uptake-1 inhibition (7). Presuming this effect of dopamine 3 µg/kg/min, to be more pronounced, it might be possible that dopamine 3 µg/kg/min results via this pathway in higher plasma norepinephrine levels than dopamine 1 µg/kg/min (8). Yet another explanation presumes that higher doses of dopamine may enhance the release of endogenous norepinephrine (9). Compared to dopamine 1 µg/kg/min, dopamine 3 µg/kg/min may lead to more pronounced vasodilatation via DA-1 receptor stimulation, which results in enhanced sympathetic activity and can in this way lead to a compensatory increase in norepinephrine levels. However, during infusion of dopamine 3 µg/kg/min blood pressure was not lower than during infusion of dopamine 1 µg/kg/min. Recently Deighton showed that part of the (inotropic) effect of dopamine is indirect via release of endogenous norepinephrine in contrast to epinephine (10), which is in accordance with previous publications (11, 12). Thus, whereas for dopamine 1 µg/kg/min the inhibitory effects on plasma norepinephrine predominate, inhibitory effects of dopamine 3 µg/kg/min on the release of norepinephrine through DA-2 dopamine and α-2 adrenergic receptors might be obscured by the decreased re-uptake of norepinephrine through uptake-1 inhibition or enhanced release or synthesis of endogenous norepinephrine. This dose dependency may even be more relevant in pathological conditions like congestive heart failure (CHF), where at rest plasma norepinephrine levels are already elevated as a reflection of increased sympathetic nervous system activity (13). So, when a decrease in plasma norepinephrine levels might be of benefit in diseases like CHF, a still lower dose of dopamine infusion (1 µg/kg/min) than normally used is perhaps of value. This dose of dopamine already increases renal hemodynamics and natriuresis in studies in healthy volunteers (14, 15). If such a dose dependent balance of contrasting effects of dopamine indeed exists, dopamine antagonists might be of help to un-

<table>
<thead>
<tr>
<th>Syst. Pressure (mmHg)</th>
<th>Placebo</th>
<th>Dopamine 1 1 µg/kg/min</th>
<th>Dopamine 3 3 µg/kg/min</th>
<th>Dopamine 1 Domperidone</th>
<th>Dopamine 3 Domperidone</th>
</tr>
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<tbody>
<tr>
<td>from 147±6 to 170±6</td>
<td>from 130±3 to 158±4</td>
<td>from 140±3 to 168±6</td>
<td>from 142±7 to 163±9</td>
<td>from 141±5 to 176±8</td>
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<td>Diast. Pressure (mmHg)</td>
<td>from 79±5 to 100±6</td>
<td>from 72±4 to 88±4</td>
<td>from 77±2 to 86±3</td>
<td>from 76±5 to 88±6</td>
<td>from 71±5 to 86±4</td>
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<tr>
<td>from 97±5 to 119±6</td>
<td>from 88±4 to 107±4</td>
<td>from 93±2 to 108±3</td>
<td>from 93±5 to 108±6</td>
<td>from 89±5 to 110±4</td>
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<tr>
<td>Mean Pressure (mmHg)</td>
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<td>from 59±4 to 67±4</td>
<td>from 60±3 to 66±5</td>
<td>from 61±4 to 71±4</td>
<td>from 61±5 to 69±5</td>
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<td>from 1.18±0.18 to 1.97±0.28</td>
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<td>from 1.04±0.18 to 2.02±0.24</td>
<td>from 0.97±0.14 to 1.53±0.23</td>
<td>from 0.79±0.12 to 2.17±0.49</td>
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ravel it. Addition of domperidone to dopamine 1 μg/kg/min indeed abolished the inhibitory effects of dopamine 1 μg/kg/min on plasma norepinephrine levels. This is in accordance with the hypothesis that this effect on plasma norepinephrine levels is due to stimulation of DA-2 dopamine receptors. Addition of domperidone did not alter the effects of dopamine 3 μg/kg/min on plasma norepinephrine levels in our present study. However also α-2 adrenergic receptor stimulation might decrease plasma norepinephrine levels. Perhaps during dopamine 3 μg/kg/min, there is also more α-2 adrenergic stimulation compared to dopamine 1 μg/kg/min. Therefore, the effect of domperidone might be more pronounced during infusion of dopamine 1 than of dopamine 3 μg/kg/min. On the other hand in a previous study, we used exercise as a model to activate the sympathetic nervous system and observed a significantly enhanced increase in the plasma norepinephrine levels during infusion of dopamine i.v. 3 μg/kg/min and domperidone 30 mg orally compared to all other study-days, without an effect on the increase in systolic, mean arterial blood pressure or lactate levels. This is also in accordance with the results of a study of Mannelli et al. (16). That we did not observe a significant effect of the addition of domperidone to dopamine 3 μg/kg/min in our present study, in contrast to our previous study, might perhaps be due methods used to stimulate the sympathetic nervous system. Indeed during exercise we observed much higher plasma norepinephrine levels (mean 15.48 ± 2.14 nmol/l) than during the cold pressor test (mean 1.75 ± 0.91 nmol/l). Therefore, the effect of domperidone might be more pronounced during exercise than during the cold pressor test. Lastly, a type 2 error can not be excluded. We conclude that in healthy volunteers dopamine 1 μg/kg/min infusion blunts the increase in plasma norepinephrine levels during a cold pressor test compared to either placebo or dopamine 3 μg/kg/min infusion. The addition of domperidone abolished the lowering effect of dopamine 1 μg/kg/min compared with placebo.

References