Accentuated hypotensive effect of sodium nitroprusside in man after captopril

G. L. JENNINGS, J. S. GELMAN, J. R. STOCKIGT and P. I. KORNER
Baker Medical Research Institute, Clinical Research Unit and Downie Metabolic Unit, Alfred Hospital, Prahran, Victoria, Australia

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Summary

1. The effects of graded intravenous infusions of sodium nitroprusside on resting blood pressure and heart rate and on the reflex changes in these variables evoked by a standardized Valsalva manoeuvre were studied in six normal subjects. The effects of nitroprusside on the above variables were also studied after pretreatment with captopril, to allow assessment of the role of angiotensin II.

2. Nitroprusside given in doses ranging from 7.5 to 150 \( \mu \text{g/min} \) elicited dose-related decreases in resting blood pressure and rise in heart rate and in plasma renin activity (PRA). After pretreatment with captopril, nitroprusside could not be given at doses above 60 \( \mu \text{g/min} \) without producing an unacceptable fall in blood pressure. The rise in heart rate in response to a given dose of nitroprusside was little altered after captopril.

3. Blood pressure and heart rate were studied during the last 10 s of the Valsalva manoeuvre. Before captopril the normal response (maintenance of blood pressure with tachycardia) was not altered by any dose of nitroprusside. Captopril alone also had no effect on the response but, with captopril plus high dose nitroprusside, mean arterial pressure during the manoeuvre decreased significantly, indicating impairment of reflex constrictor response.

4. These findings support the proposition that the angiotensin II response normally limits the fall in blood pressure during vasodilator therapy. We conclude that the greater fall in blood pressure and the impaired constrictor response to the Valsalva manoeuvre during nitroprusside infusion at moderate doses, in the presence of captopril, is due to the effect of the latter on the renin–angiotensin system.

5. A practical consequence of the present findings is that combined use of captopril and arterial vasodilators requires reduction in the dose of the latter drug. Awareness of this interaction may avert hypotension and could also allow nitroprusside infusion for longer periods without toxicity.

Key words: captopril, nitroprusside, renin–angiotensin system, Valsalva test, vasodilators.

Abbreviations: MAP, mean arterial pressure; PRA, plasma renin activity.

Introduction

Vasodilator drugs are finding an increasing use in the management of both acute and chronic cardiac failure [1, 2] and hypertension. As well as their effects on the peripheral vasculature, these drugs also lead to increased activity of the renin–angiotensin system [3]. Studies with competitive angiotensin II antagonism suggest that increased formation of angiotensin II may oppose the fall in blood pressure that results from the direct action of the vasodilator on vascular smooth muscle [4]. In order to define this relationship further we have studied the effect of captopril (which inhibits the conversion of angiotensin I into angiotensin II) on the relationship between dosage of the vasodilator sodium nitroprusside and changes in resting arterial blood pressure.
pressure and heart rate, in normal subjects. We have also examined to what extent different doses of nitroprusside modify the reflex changes evoked by a standard Valsalva manoeuvre both before and after captopril.

Methods

Six normal male subjects participated in the study, which was approved by the Alfred Hospital Clinical Investigation Committee. Their average age was 22 years (range 20–24 years). All studies were performed in the morning after a light breakfast and each subject completed the study on 1 day. The protocol consisted of intravenous infusion of several doses of nitroprusside. The infusion was repeated 1 h after a single 25 mg oral dose of captopril.

Each subject was recumbent for 60 min before the study. Sodium nitroprusside (Nipride, Roche) was infused through a cannula inserted into a forearm vein. The stock solution consisted of 50 mg of nitroprusside dissolved in sodium chloride solution (0.9%; 150 mmol/l: saline) and the dose was varied by altering the rate of infusion of this solution with a pump. The initial infusion rate of 7.5 μg/min was subsequently increased every 10 min to 15, 30, 60 and 150 μg/min. Heart rate was measured continuously during the infusion from the R–R interval of the electrocardiogram. Blood pressure was also measured throughout the infusion from a cannula in the right brachial artery, with Gould-Statham transducers. After the completion of the initial nitroprusside infusion there was a 30 min rest period, after which the subject ingested a single 25 mg tablet of captopril. One hour later control measurements were performed and graded doses of nitroprusside were then administered as before. In two subjects mean arterial pressure (MAP) fell below 50 mmHg after 30 μg/min and higher doses were not therefore given. In four subjects the protocol was repeated on another day with two nitroprusside infusions performed 1 h apart, but placebo was administered instead of captopril after the first infusion.

Before each infusion and after 8 min at each dose of nitroprusside a standardized Valsalva manoeuvre was performed as described previously [5]. During the manoeuvre a column of water equivalent to a pressure of 20 mmHg was supported for 30 s by forced expiration; a small leak in the system prevented closure of the glottis and ensured that the expiratory pressure was transmitted to the chest. Heart rate and phasic and mean arterial pressures were recorded continuously during, and for 90 s after, the Valsalva manoeuvre. On each occasion, the classic four phases of the normal Valsalva response could be distinguished [6]. At the beginning of forced expiration there was a small rise in mean arterial pressure, which was followed by a transient fall below resting in the next 5–10 s (early phase). Mean arterial pressure then returned to near resting values during the last 5–10 s of forced expiration (late phase 2). At the end of forced expiration there was a small transient fall in mean blood pressure (phase 3) followed by a rapid rise above the pre-manoeuvre level (phase 4 or ‘overshoot’). The main effects studied were those of the heart rate and mean blood pressure occurring during the late phase 2 of the manoeuvre, before release of forced expiratory pressure [5, 7].

Plasma renin activity (PRA) was measured by radioimmunoassay [8] from venous samples taken at the end of the control periods and after each dose of nitroprusside. PRA in sodium-replete normal subjects ranged from 0.3–1.4 ng h⁻¹ ml⁻¹, expressed in terms of angiotensin I reference standard 71/328 [9].

Statistical analysis of all responses was by analysis of variance of results within subjects [10]. Standard error of the difference (SED) between treatments (within subjects) was (S^2EMS/n)^0.5, where EMS is the error mean square and n the number of subjects.

Results

Resting variables

Sodium nitroprusside infusions resulted in a dose-related fall in MAP, rise in heart rate and in plasma renin activity (Fig. 1). At the highest dose (150 μg/min) MAP had fallen by 34 mmHg (35%) and heart rate had increased by 31 beats/min (53%). PRA had increased almost eightfold to 4.89 ng of angiotensin I h⁻¹ ml⁻¹, although the increase was mainly at the two highest doses (Fig. 1).

One hour after 25 mg of captopril the average MAP was 8 mmHg lower than the control value before the initial nitroprusside infusion (P < 0.025). Heart rate was slightly higher than control in four of six subjects, but the average difference (6.3, SEM 4.4, beats/min) was not statistically significant. After captopril each dose of nitroprusside produced a significantly greater fall in MAP (P < 0.001). At an infusion rate of 30 μg/min, the MAP decreased below the resting value by 13 mmHg (16%) before captopril and 22 mmHg (26%) after captopril (P < 0.025). Because MAP had fallen below 50 mmHg we did
Nitroprusside after captopril

Fig. 1. Mean arterial blood pressure (MAP), heart rate and plasma renin activity (PRA) at the various doses of nitroprusside before and after captopril. Error bars indicate ± SEM within subjects from the analysis of variance.

Table 1. Nitroprusside effects before and after placebo

<table>
<thead>
<tr>
<th>Sodium nitroprusside (µg/min)</th>
<th>0</th>
<th>7.5</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>76</td>
<td>79</td>
<td>83</td>
<td>85</td>
<td>91</td>
<td>103</td>
</tr>
<tr>
<td>1 h</td>
<td>72</td>
<td>72</td>
<td>73</td>
<td>80</td>
<td>84</td>
<td>108</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>86</td>
<td>85</td>
<td>84</td>
<td>82</td>
<td>76</td>
<td>61</td>
</tr>
<tr>
<td>1 h</td>
<td>85</td>
<td>85</td>
<td>82</td>
<td>82</td>
<td>75</td>
<td>66</td>
</tr>
</tbody>
</table>

SED, Standard error of difference.

not give nitroprusside doses higher than 30 µg/min in two of six subjects or higher than 60 µg/min in the remaining subjects. In contrast to the blood pressure effects, the increase in heart rate after nitroprusside was not significantly affected by pretreatment with captopril; i.e. heart rate was 18 beats/min (30%) higher than control after 30 µg of nitroprusside/min alone, but 21 beats/min (31%) higher than after captopril alone at the same dose of nitroprusside during the second infusion. Plasma renin activity was increased after captopril even before administration of nitroprusside (P < 0.05) (Fig. 1). In addition, in the presence of captopril a given dose of nitroprusside produced more marked rise in PRA than before captopril (P < 0.001).

Mean arterial pressure during the infusions performed before and after placebo were closely similar at each of the nitroprusside doses (Table 1). There was a tendency for heart rate to be lower before nitroprusside and at the low infusion rates of nitroprusside. This difference was not significant before nitroprusside or at any single dose of nitroprusside, but when the sums of squares from the analysis of variance were partitioned for comparison of the heart rate at rest, and with 7.5 and 15 µg/min before and after placebo, the difference was significant (P < 0.05).

Valsalva responses

During the late phase 2 of the Valsalva response before captopril, there was normal restoration of MAP either to or slightly above the level just before forced expiration (Table 2), in
agreement with previous findings. Restoration of MAP during the Valsalva manoeuvre was not affected by the various doses of nitroprusside during the first infusion. During the Valsalva manoeuvre before nitroprusside heart rate increased during the late phase 2 by 18.6 ± 5.5 beats/min above the resting value before forced expiration. The magnitude of the tachycardia during this phase of the Valsalva response was unaffected by nitroprusside (Table 2), despite the higher heart rate before the manoeuvre, at each dose of nitroprusside.

Neither blood pressure nor heart rate changes of the Valsalva response were altered by captopril alone (Table 2). However, when nitroprusside was administered after pretreatment with captopril there was a dose-related failure to restore the MAP during phase 2 to pre-Valsalva levels at the highest doses of nitroprusside (Table 2). The fall of 13.4 ± 5.5 mmHg in MAP below the pre-manoeuvre value when nitroprusside was given at 30 µg/min was significantly greater than the change found with the same dose of nitroprusside before captopril (P < 0.001). The lack of maintenance of blood pressure during the Valsalva manoeuvre after captopril and nitroprusside was not accompanied by a significantly greater tachycardia and the change in heart rate tended if anything to be somewhat smaller than with nitroprusside alone (Table 2).

Discussion

Our results indicate that nitroprusside produced dose-related increases in PRA, confirming previous observations that it stimulates the renin–angiotensin system [11]. The findings suggest that increased angiotensin II production normally limits the hypotensive effect of nitroprusside since nitroprusside evoked a significantly greater fall in blood pressure after captopril. The greater fall in blood pressure from the control value after captopril was most pronounced at the two highest doses of nitroprusside tested (30 and 60 µg/min), where stimulation of the renin–angiotensin system was greatest. At these doses the fall in blood pressure was close to the limit of acceptability making it unsafe to study higher doses.

An alternative explanation for the greater fall in blood pressure after captopril may relate to increased production of endogenous vasodilators, e.g. kinins [12, 13] or prostaglandins [14]. A point in favour of this explanation was that captopril lowered resting blood pressure in the present study. However, experimental design may have contributed to this, because the effects of nitroprusside plus captopril were always studied after nitroprusside alone. The absence of any fall in blood pressure in subjects studied after placebo make the possibility of a time-related effect on blood pressure unlikely although such an effect is not fully excluded.

It is notable that Swartz et al. [14] found no relationship between kinin levels and fall in blood pressure after captopril. Accordingly, if the greater fall in blood pressure after captopril were due to increased vasodilator, one would have expected a greater blood pressure fall after captopril at all doses of nitroprusside, rather than just at the two highest doses. Furthermore, maintenance of blood pressure during the Valsalva manoeuvre after captopril was impaired only at the two highest doses of nitroprusside, again suggesting that the effect was related to the increase in activity of the renin–angiotensin system (see below). For these reasons it appears more likely that enhanced activity of the renin–angiotensin system, rather than reduced formation of kinins or prostaglandins, was limiting the hypotensive effect of nitroprusside.

Over the rather narrow dose range of nitroprusside tested after captopril, there was no enhancement of the nitroprusside-induced tachycardia despite the greater fall in blood pressure. This suggests some alteration in properties of the

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**TABLE 2. Response to Valsalva manoeuvre: change from value before forced expiration of 20 mmHg for 30 s**

<table>
<thead>
<tr>
<th>Sodium nitroprusside (µg/min)</th>
<th>0</th>
<th>7.5</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>150</th>
<th>SED₁</th>
<th>SED₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>△ MAP Control</td>
<td>+2.8</td>
<td>+2.2</td>
<td>+2.2</td>
<td>+4</td>
<td>+2.8</td>
<td>-3.8</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>-1.6</td>
<td>-1</td>
<td>-5.4*</td>
<td>-13.4**</td>
<td>-3.8</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>△ Heart rate Control</td>
<td>+18.6</td>
<td>+15.9</td>
<td>+17.6</td>
<td>+16.6</td>
<td>+20</td>
<td>+33.9</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>+17.4</td>
<td>+12.7</td>
<td>+16</td>
<td>+10.4</td>
<td>---</td>
<td>---</td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

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SED₁, Standard error of difference between any two columns from analysis of variance; SED₂, standard error of the difference between values before and after captopril at each dose of nitroprusside, within subjects. *P < 0.05 for difference before and after captopril at a given nitroprusside dose; **P < 0.01.
baroreceptor reflexes controlling heart rate. Reduction in gain of baroreceptor–heart rate reflexes has been described through the central action of angiotensin II [15, 16]. In the present study we used the Valsalva reflex to study change in heart rate rather than the effects of changes in blood pressure induced by vasoactive drugs [17, 18].

The afferents involved in the Valsalva manoeuvre involve mainly intrathoracic baroreceptors, including the aortic baroreceptors and cardiac receptors [19], whereas the changes produced by vasoactive drugs are probably mediated through carotid and aortic baroreceptors plus a smaller contribution from cardiac receptors [20]. Our finding that the heart rate response during the Valsalva manoeuvre at 30 and 60 µg of nitroprusside was if anything smaller, despite the larger fall in blood pressure after captopril, suggests some reduction in reflex gain, consistent with the known effects of angiotensin II on this reflex [15, 16, 21].

After captopril the blood pressure was no longer satisfactorily maintained during the Valsalva manoeuvre at the highest doses of nitroprusside. Previous work has shown that the normal maintenance of blood pressure close to the pre-maneuver value is due to a vasoconstrictor response mediated through the sympathetic nerves and is normally associated with a rise in total peripheral resistance [5]. Before the administration of captopril it is possible that increased release of angiotensin II during the manoeuvre might have contributed directly to the maintenance of blood pressure. This seems unlikely (i) because of the short duration of the Valsalva manoeuvre and (ii) because of the absence of any impairment in the blood pressure response to the manoeuvre after captopril alone or after captopril plus the lowest dose of nitroprusside. These considerations make it likely that at moderate and high doses of nitroprusside some of the circulating angiotensin II exerted a direct facilitatory action on sympathetic activity, through central nervous mechanisms which assisted maintenance of blood pressure when the Valsalva manoeuvre was performed.

The results of the present study have important clinical implications. Firstly, the use of captopril, in combination with nitroprusside or other vasoactivators which stimulate the renin–angiotensin system, may reduce total peripheral resistance more than either agent alone and thus be of greater therapeutic benefit. In a normal subject captopril can be regarded as blocking increased production of angiotensin II, which is a homeostatic response after vasodilators. In some patients with chronic cardiac failure angiotensin II levels may already be increased even before administration of vasodilators and in such patients captopril effects may be particularly exaggerated [22]. Furthermore, toxicity is a major problem in the prolonged clinical use of nitroprusside at high doses in the management of acute cardiac failure. The combination of captopril plus nitroprusside allows the use of smaller doses of nitroprusside to achieve a given therapeutic effect and may permit its administration for larger periods. It follows also that patients taking chronic captopril therapy, who require nitroprusside, should receive lower starting doses to avoid severe hypotension.

References


