The effect of magnesium sulphate infusion on circulating catecholamine levels in severe gestational proteinuric hypertension

A report of 8 cases

M. J. ENGLAND, V. R. PANZ, B. I. JOFFE, R. M. TOUYZ, R. SHIRES, H. C. SEFTEL

Summary

The effect of magnesium sulphate (MgSO₄) infusion on blood pressure and circulating venous catecholamine levels in 8 patients with severe gestational proteinuric hypertension is described. A significant fall in blood pressure was noted after MgSO₄ infusion; the maximal fall in diastolic blood pressure correlated with the greatest rise in serum magnesium levels (P < 0.04). No significant change was observed in mean venous plasma adrenaline or noradrenaline levels after MgSO₄ infusion, although the mean dopamine concentration declined significantly. It is concluded that the decrease in systemic vascular resistance after MgSO₄ infusion in gestational proteinuric hypertension is mediated predominantly by mechanisms other than a change in circulating catecholamine levels.

Patients and methods

The protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand and the Pharmacy and Therapeutics Committee of Baragwanath Hospital.

Primigravid patients presenting with severe GPH, defined as a blood pressure > 140/90 mmHg together with proteinuria > 0.3 g/l, met the inclusion criteria for the study. Patients were excluded if they had any history related to hypertensive disease, were known to be hypertensive before conception, were morbidly obese, had cardiorespiratory problems, diabetes, a history of chronic drug intake or obstetric complications other than GPH.

Eight patients were recruited into the study. All were classified as having severe GPH after a 1-hour pre-study observation period, and all subsequently required termination of pregnancy because of complications. All were admitted to the unit, an intravenous catheter was placed in the left forearm and kept patent by a normal saline infusion run at 10 ml/h. Patients were then rested in the right lateral position for 30 minutes. Blood pressure was measured non-invasively every 5 minutes throughout this basal period. A Critikon non-invasive blood pressure machine was employed; calibration against a mercury sphygmomanometer was checked before its use on each patient. Two venous blood samples were taken without constriction, 5 minutes apart, at the end of this basal period and were placed in tubes without anticoagulant for serum magnesium estimations, and in tubes containing ethylene glycol tetra-acetic acid and glutathione for plasma catecholamine measurements. A bolus infusion of 6 g of MgSO₄, diluted in 200 ml of normal saline was administered intravenously over 20 minutes. Immediately afterwards, the intravenous infusion of MgSO₄ was continued at a rate of 2 g/h for 3 hours. Throughout the subsequent infusion period, the patients continued to rest in the right lateral position, blood pressure was monitored every 5 minutes and routine fetal cardiotocography was performed. No other drugs were administered during this period. Labour was not induced nor membranes ruptured and no vaginal examinations were done in any of the patients.

Further blood samples for serum magnesium and plasma catecholamine measurement were collected, without constriction, 10 minutes after starting the infusion, at completion of the bolus, and 3 hours later. The samples for plasma catecholamine measurement were centrifuged immediately and the separated plasma aliquots stored at −70°C until assayed within 10 weeks for dopamine, adrenaline and noradrenaline. Plasma catecholamine concentrations were determined by a radioenzymatic method, using reagents supplied by Amersham International, UK. All measurements for an individual patient were analysed in duplicate in the same assay to avoid interassay variation. The intra-assay coefficients of variation ranged from 4% to 12% for individual plasma catecholamine levels. The lower limits of sensitivity for the assay were 2 - 5 ng/l for adrenaline and noradrenaline, and 15 - 20 ng/l for dopamine.

Samples for serum magnesium estimations were allowed to clot and the separated sera stored at −70°C until measured by atomic absorption spectrophotometry; the intra-assay coefficient of variation for the method was < 2%.

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Statistical analysis. Basal concentrations for each patient were calculated from the arithmetic mean of the two basal samples; basal blood pressure was similarly derived from the final two baseline readings. Data were analysed by Student's paired t-test and the signed-rank test for non-parametric data. Pearson correlations were calculated to assess the relationship between some of the variables. The overall maximum change from the mean basal level was termed the Δ change. All mean values are expressed as ± 1 SD.

Results

Table I summarises individual clinical details as well as basal serum magnesium and plasma catecholamine concentrations in the 8 patients. The mean maternal age was 29.1 ± 4.4 years and gestational age 33.3 ± 2.9 weeks. The mean basal blood pressure recorded in these 8 patients was 181 ± 19 mmHg systolic and 122 ± 12 mmHg diastolic. Proteinuria exceeded 1.0 g/l on semiquantitative analysis in all cases.

Effect of MgSO₄ infusion on basal blood pressure reading (Table II)

The mean basal serum magnesium concentration was found to be 0.73 ± 0.15 mmol/l. It increased sharply after the bolus dose of magnesium sulphate to 3.44 ± 1.32 mmol/l at 20 minutes (P < 0.001), and the level remained significantly elevated at 3 hours. This was accompanied by progressive and significant falls in both the mean systolic and diastolic blood pressure readings throughout the 3-hour infusion period. In addition, there was a significant inverse correlation between the Δ increase in serum magnesium and Δ fall in diastolic blood pressure in the 8 patients (P < 0.04).

Effect of MgSO₄ infusion on basal plasma catecholamine concentrations (Table III)

Mean basal levels of dopamine, adrenaline and noradrenaline were either within, or slightly above, the normal basal range for our laboratory. Only the mean plasma dopamine concentration showed a progressive and significant decline during the 3-hour infusion period. Neither the mean plasma adrenaline nor the noradrenaline values changed significantly in that time. There was no significant correlation between the Δ increase in serum magnesium, and Δ fall in any of the 3 plasma catecholamine levels in the 8 patients studied.

Discussion

The major aim of the present investigation was to establish whether the fall in blood pressure induced by infusing large amounts of MgSO₄ in women with GPH was associated with a reduction in circulating catecholamine levels. This might have been anticipated from in vitro investigations,² animal experiments,¹⁰ and clinical studies,¹¹ ¹² where magnesium has been shown to markedly suppress the release of catecholamines from the adrenal gland and peripheral nerve terminals.

However, MgSO₄ did not alter the plasma levels of adrenaline and noradrenaline in these patients, despite raising the serum magnesium level substantially and causing a significant fall in blood pressure. Although the mean plasma dopamine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maternal age (yrs)</th>
<th>Gestation age (wks)</th>
<th>Basal blood pressure (mmHg)</th>
<th>Serum magnesium (mmol/l)</th>
<th>Plasma dopamine (ng/ml)</th>
<th>Plasma adrenaline (ng/ml)</th>
<th>Plasma noradrenaline (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>30</td>
<td>155</td>
<td>0.91</td>
<td>371</td>
<td>49</td>
<td>128</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>36</td>
<td>180</td>
<td>0.72</td>
<td>181</td>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>36</td>
<td>170</td>
<td>0.55</td>
<td>940</td>
<td>110</td>
<td>209</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>31</td>
<td>180</td>
<td>0.56</td>
<td>552</td>
<td>41</td>
<td>123</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>37</td>
<td>190</td>
<td>0.53</td>
<td>297</td>
<td>74</td>
<td>138</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>34</td>
<td>180</td>
<td>0.84</td>
<td>433</td>
<td>87</td>
<td>115</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>32</td>
<td>220</td>
<td>0.66</td>
<td>326</td>
<td>107</td>
<td>392</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>30</td>
<td>170</td>
<td>0.67</td>
<td>420</td>
<td>55</td>
<td>258</td>
</tr>
</tbody>
</table>

Statistical significance compared to basal:
* P < 0.05.
** P < 0.01.
*** P < 0.001.
concentration fell by about 50% during the infusion, it is difficult to envisage how magnesium could have induced a selective reduction in dopaminergic release without affecting the other catecholamines. Moreover, the relationship between circulating plasma dopamine activity and systemic blood pressure in human subjects is uncertain.\(^1\)

It is conceivable that the infusion of magnesium may have prevented a *rise* in circulating catecholamine levels during the study as a result of the discomfort, although slight, of repeated blood pressure monitoring. This point could have been clarified if a control saline infusion had been administered to some of the women with GPH instead of magnesium sulphate. However, in view of the serious nature of their clinical state, it was not considered ethical to do so.

Our data support findings by others that venous catecholamine levels are largely normal in patients presenting with GPH.\(^3,14\) Conflicting observations may have been caused by studying a subset of patients who had elevated catecholamine levels.\(^15\) The precise role of the autonomic nervous system in this disease remains unclear.

In conclusion, our study suggests that the decrease in systemic vascular resistance after MgSO\(_4\) infusion in women with GPH is mediated predominantly by mechanisms other than the suppression of circulating plasma catecholamine levels. These mechanisms could involve both a direct relaxant action of magnesium on peripheral small arteries and a reduction in vascular reactivity in response to catecholamine stimulation.\(^16\) Also, the state of activation of the renin-angiotensin system may be important.\(^17\)

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**REFERENCES**


**TABLE III. EFFECTS OF MgSO\(_4\) INFUSION ON MEAN BASAL PLASMA CATECHOLAMINE CONCENTRATIONS**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>10 min</th>
<th>20 min</th>
<th>3 hours</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine (ng/l)</td>
<td>440 ± 229</td>
<td>395 ± 233</td>
<td>268 ± 153*</td>
<td>245 ± 154*</td>
<td>110 - 400</td>
</tr>
<tr>
<td>Adrenaline (ng/l)</td>
<td>68 ± 32</td>
<td>54 ± 27</td>
<td>65 ± 28</td>
<td>41 ± 29</td>
<td>23 - 53</td>
</tr>
<tr>
<td>Noradrenaline (ng/l)</td>
<td>178 ± 106</td>
<td>151 ± 75</td>
<td>171 ± 87</td>
<td>152 ± 141</td>
<td>120 - 360</td>
</tr>
</tbody>
</table>

Statistical significance compared to basal: *P < 0.01