Correspondence

British Heart Journal, 1979, 42, 362–363

Diazoxide in treatment of primary pulmonary hypertension

Sir,

After reading the report by Wang et al. in the British Heart Journal (1978, 40, 572–574), we attempted a trial of diazoxide in a patient with primary pulmonary hypertension. The outcome suggests caution in the use of this drug in such patients.

A 39-year-old woman with severe pulmonary hypertension with no apparent cause had previously undergone unsuccessful trials of oxygen, nitroprusside, isoprenaline, and tolazoline during cardiac catheterisation. In August 1978 diazoxide was injected into the main pulmonary artery, and haemodynamic measurements were taken 5 minutes after each dose using the procedure described by Wang et al. (1978). The results are given in the Table.

<table>
<thead>
<tr>
<th>Diazoxide</th>
<th>Heart rate (beats/min)</th>
<th>CO (l/min)</th>
<th>Pulmonary arterial pressure (mmHg)</th>
<th>Left ventricular pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>90</td>
<td>1.1</td>
<td>103/49 (67)</td>
<td>140</td>
</tr>
<tr>
<td>45 mg</td>
<td>95</td>
<td>1.4</td>
<td>110/60 (74)</td>
<td>134</td>
</tr>
<tr>
<td>90 mg</td>
<td>95</td>
<td>1.4</td>
<td>112/57 (76)</td>
<td>134</td>
</tr>
<tr>
<td>180 mg</td>
<td>113</td>
<td>1.6</td>
<td>117/61 (81)</td>
<td>137</td>
</tr>
</tbody>
</table>

With the 300 mg injection the patient coughed, developed generalised seizures, ventricular tachycardia, and hypotension unresponsive to immediate resuscitation, including adequate ventricular pacing and pressor agents. Necropsy confirmed the diagnosis of primary (plexigenic) pulmonary hypertension.

Diazoxide administered by peripheral vein has been found to lower pulmonary artery pressure and resistance in patients with pulmonary hypertension (Just and Stein, 1969). The intravenous solution is highly alkaline (pH 11.6) and known to be irritating to vascular tissue. Given the potentially lethal response to pulmonary artery injections in patients with primary pulmonary hypertension (Snider et al., 1973), we wonder if pulmonary artery injection should be avoided in future trials of this drug.

Finally, our patient had a progressive rise in pulmonary artery pressures at lower doses. Since the diazoxide binding capacity of patients with normal serum albumin is 160 mg/l (Sellers and Koch-Weser, 1973), the 300 mg injection presumably results in a sudden large increase in unbound drug, and consequently in drug effect. We would be interested to learn if the patients reported by Wang et al. showed progressive improvement with lower doses. If so, the pattern of response might predict whether the 300 mg injection would be beneficial or hazardous.

Joseph Michael Rubino and John S. Schroeder, Stanford University Medical Center, Stanford, California, USA.

References


This letter was shown to the authors, who reply as follows:

Sir,

Drs Rubino and Schroeder are right to emphasise the dangers of intrapulmonary arterial injections of vasodilators in primary pulmonary hypertension. One of us has in the past had a fatality after injection of tolazoline. Every effort must, therefore, be made to monitor the procedure step by step, and it was for this reason we measured the pulmonary and systemic resistances after each dose allowing time for a stable state to be achieved. At each stage values for heart rate, pulmonary and systemic arterial pressures, cardiac output, pulmonary and...
systemic arterial resistances, and right and left ventricular stroke and minute work were calculated.

In the case described by Drs Rubino and Schroeder there is one major indicator of possible danger. Their data suggest that up to a level of 180 mg there had been no significant fall in the pulmonary arterial resistance despite a fall in the systemic resistance. The rise in cardiac output and heart rate and in the pulmonary arterial pressure implies a substantial increase in right ventricular minute work. This may well be the critical factor.

In 3 of our 4 cases a drop in pulmonary vascular resistance was obvious at the lower dose levels, and even in these patients a slight rise in right ventricular work occurred. If no such fall in resistance occurs, despite a drop in systemic pressure, it may well be dangerous to go on. We were, perhaps, at fault in our paper in not making this point more emphatically.

There is a further indicator in the patient of Drs Rubino and Schroeder that the response to diazoxide might well have been expected to prove unsatisfactory. She had previously failed to respond to intrapulmonary arterial injections of nitroprusside. Nitroprusside is at least as strong a vasodilator at arteriolar level as diazoxide. We have no experience in the use of this drug and we do not know, therefore, whether failure to respond to nitroprusside necessarily predicts failure to respond to diazoxide but it may well be so.

Drs Rubino and Schroeder are correct in stating that the 300 mg injection will lead to a temporary large increase in the level of unbound diazoxide. This, however, is not necessarily disadvantageous providing the trend up to that point had been favourable.

Primary plexigenic pulmonary hypertension is a highly lethal condition and such patients tolerate any invasive investigation badly. The proportion helped by diazoxide may be small but it seems to us essential that the drug is fully and carefully evaluated. Despite the risks of invasive investigations in such patients we believe that haemodynamic evaluation of the probable response is essential if oral maintenance treatment is being contemplated.

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Diazoxide in treatment of primary pulmonary hypertension.

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*Br Heart J* 1979 42: 362-363
doi: 10.1136/hrt.42.3.362

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