SOME CARDIOVASCULAR EFFECTS OF ORNITHINE-8-VASOPRESSIN: A NEW SURGICAL VASOCONSTRICTOR AGENT

A. J. Coleman and L. W. Baker

SUMMARY

The cardiovascular effects of ornithine-8-vasopressin (POR-8), a new systemic and local vasoconstrictor, have been measured in 12 patients under anaesthesia with either nitrous oxide, or nitrous oxide and 1% halothane. No cardiac dysrhythmias occurred. Peripheral vascular resistance and mean arterial blood pressure were increased and heart rate and cardiac output were reduced. It is suggested that POR-8 be used as a local vasoconstrictor agent during surgery in preference to adrenaline.

Blood loss in surgery may be effectively controlled by the infiltration of adrenaline. Following subcutaneous or submucosal injection circulating plasma levels of adrenaline rise however (Brindle, Gilbert and Millar, 1957) and it is well established that this factor is associated with cardiac dysrhythmias and even cardiac arrest. Anaesthesia using the volatile halogenated hydrocarbons or cyclopropane increases this risk as do hypoxaemia and acidemia (Hall and Norris, 1958; Katz, Matteo and Papper, 1962; Matteo, Katz and Papper, 1962; Katz, 1965).

These experiences have prompted the search for a safer local vasoconstrictor. Ornithine-8-vasopressin (POR-8), a synthetic derivative of the natural neurohypophyseal hormone, has recently been introduced as a systemic and local vasoconstrictor. It is an octapeptide with five amino acids in a cyclic grouping and a side chain of three amino acids, differing from vasopressin by virtue of ornithine substitution for lysine in the side chain. In comparison with natural vasopressin this drug has enhanced pressor actions and much reduced antidiuretic effects (Personal communication, R. A. Asherson, 1972, Sandoz Products).

The effectiveness of POR-8 as a local vasoconstrictor is well established (Rea, 1969; Nielsen and Valentin, 1970; McCaffrey, 1970; Klingenstrom, Nylen and Westermark, 1967) but there have been no reports describing cardiovascular effects of the drug. The present study was undertaken to investigate the effects of intravenous administration of POR-8 to anaesthetized man.

METHODS

Twelve male patients, aged 20–40, who gave their written consent, were investigated prior to the onset of elective minor surgery. Body weights ranged from 50 to 70 kg. All patients were clinically free of cardiopulmonary disease. Premedication, consisting of papaveretum 20 mg, and hyoscine 0.4 mg, was given by intramuscular injection 1 hour prior to commencement of the studies.

Plastic catheters were inserted percutaneously under local analgesia into the radial artery and into the right atrium from a suitable right antecubital vein. Pressures were measured by Statham gauge transducers supported 3" above the surface of the operating table, and recorded continuously on a Philips 3T recorder. Heart rate was measured using a SAN E12 D16 pulse meter and a finger photo cell. A lead 2 e.c.g. was recorded throughout the study. Cardiac output was measured by dye dilution using indocyanine green and the Philips X01000 combined oximeter/densitometer cuvette. Arterial oxygen saturation and haemoglobin were measured during each cardiac output estimation.

At the conclusion of each experiment, the cardiac output densitometer was calibrated using each patient's own blood and known doses of cardiac green. Cardiac output was calculated using the method of Williams, O'Donovan and Wood (1966), to prepare an appropriate program for an Olivetti digital computer. Total peripheral vascular resistance (PVR) was calculated from the formula of Aperia (1940).

\[ PVR = \frac{\text{mean arterial pressure (mm Hg)}}{\text{cardiac output (l./min)}} \times 80 \text{ dyn sec cm}^{-1} \]

End-expired carbon dioxide levels were measured continuously using the Beckman LBI infra-red gas analyser.

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Tests of statistical significance were applied to the mean differences in measurement made in the control periods preceding administration of POR-8, and after by applying Student's t-tests to the paired comparison.

Anaesthesia was induced in 6 patients (group I) by intravenous injection of 2.5% thiopentone 100–250 mg. Intubation of the trachea was facilitated by giving pancuronium 6 mg. Ventilation of the lungs was performed mechanically using a Manley respirator delivering nitrous oxide (70%) and oxygen (30%) at an expired minute volume sufficient to maintain the end-expired carbon dioxide at 4%.

The anaesthetic management of the remaining 6 patients (group II) was the same as group I except 1% halothane was added to the inspired gases.

Following induction of anaesthesia sufficient time was allowed for the heart rate and blood pressure to become steady. Cardiac output and arterial oxygen saturation estimations were then made at about 3-min intervals until the areas of at least two dye dilution curves appeared to agree within 10%, and the arterial oxygen saturation was steady to within 1%. Blood pressures and heart rates at this moment were noted and served as control measurements. POR-8 5 U mixed with 19 ml normal saline was given intravenously using a mechanical syringe adjusted to deliver 1 ml/min.

Control measurements were repeated 5, 10 and 20 min after commencement of injection of POR-8 in group I patients, and after the elapse of 10 and 20 min in group II patients.

Confirmation of "steady state" was successfully sought in 3 patients of each group by prolongation of the control period for 1 hour.

### RESULTS

No cardiac dysrhythmias occurred during injection of POR-8.

In both groups cardiovascular effects were apparent within 3 min of commencement of injection of POR-8, and thereafter a new "steady state" appeared to exist not only for the period of this investigation, but in many instances for a period of more than 60 min thereafter.

In group I patients (table I) the increase in systemic vascular resistance of about 700 dyn sec cm⁻² was accompanied by a significant increase in mean arterial blood pressure of more than 20 mm Hg at each period of measurement. Heart rate was significantly decreased. The cardiac output was also decreased, but this change was not significant.

In group II patients (table II) an even greater increase in peripheral vascular resistance occurred. Arterial blood pressure increased, but this change was not significant. The heart rate decreased significantly by 18 beats/min. The cardiac output was significantly reduced by about 21 l/min.

### DISCUSSION

There have been reports of cardiac dysrhythmias following the administration of adrenaline to patients anaesthetized with cyclopropane (Price et al., 1958), the volatile halogenated hydrocarbon series, (Katz, 1965), ether (Byrd, 1941; Guedel and Knoefel, 1936), and nitrous oxide (Katz, 1965). In this study no dysrhythmia occurred during the intravenous injection of POR-8 to patients anaesthetized with either nitrous oxide or halothane. The cardiovascular effects observed were fundamentally different from those associated with the administration of catecholamine.

#### TABLE I

<table>
<thead>
<tr>
<th>Observation</th>
<th>Control</th>
<th>+5</th>
<th>+10</th>
<th>+20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>96 (17.05)</td>
<td>84 (19.00)*</td>
<td>83 (20.18)**</td>
<td>78 (21.05)**</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>76 (20.80)</td>
<td>106 (3.88)***</td>
<td>98 (21.60)†††</td>
<td>96 (20.39)†††</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>3.7 (2.52)</td>
<td>8.7 (5.10)</td>
<td>8.1 (3.70)</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l./min)</td>
<td>5.3 (0.28)</td>
<td>4.5 (1.11)</td>
<td>4.3 (0.93)</td>
<td>4.4 (0.75)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>54 (9.53)</td>
<td>52 (6.89)</td>
<td>53 (10.18)</td>
<td>57 (9.88)</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>1152 (311.54)</td>
<td>1967 (439.15)**</td>
<td>1851 (423.09)**</td>
<td>1744 (274.97)***</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>92.7 (2.43)</td>
<td>92.5 (1.73)</td>
<td>93.3 (1.49)</td>
<td>93.6 (1.70)</td>
</tr>
</tbody>
</table>

Levels of significance: *P<0.05; **P<0.025; ***P<0.01; ††P<0.005; †††P<0.001.
derivatives (Coleman and Leary, 1972a, b), in which heart rate and cardiac output increase, as peripheral vascular resistance and blood pressure fall. In this study the heart rate and cardiac output fell, whilst the peripheral vascular resistance and arterial blood pressure increased. Although the mechanism of these effects was not determined, it is reasonable to postulate that as peripheral vascular resistance and blood pressure increased, reflex adjustments reduce heart rate and cardiac output.

In surgical practice 5 i.u. of POR-8 in 20–50 ml of diluent should be administered by subcutaneous or submucosal injection. Blood levels of the drug are likely to be lower than those which obtained in this study in which the intravenous route was deliberately employed in an attempt to simulate inadvertent intravenous injection.

We would suggest that POR-8 warrants consideration as an alternative to established vasoconstrictors in surgical practice, particularly in view of the apparent lack of significant cardiac effects associated with this drug.

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REFERENCES


Les effets cardiovasculaires présentés par l'ornithine-8-
vasopressine (POR-8), un nouvel agent vasoconstricteur
général et local, ont été étudiés sur le plan quantitatif
chez douze malades soumis à une anesthésie par le pro-
toxyde d'azote ou le mélange protoxyde d'azote et halo-
thane à 1%. Aucune dysrythmie cardiaque n'est survenue.
La résistance vasculaire périphérique et la pression artéri-
elle moyenne ont été augmentées et la fréquence et le
débit cardiaques, diminués. Il est suggéré que POR-8 soit
utilisé comme agent vasoconstricteur local au cours d'interventions chirurgicales et ceci, de préférence à l'adrénaline.