Cardiovascular Effects of Diazepam and Droperidol during Morphine Anesthesia

THEODORE H. STANLEY, M.D.*, GEORGE M. BENNETT, M.D., EDWARD A. LOESER, M.D.,† RYOHEI KAWAMURA, M.D., Craig R. Sentker, B.S.‡

Although large doses (0.5–3.0 mg/kg, iv) of morphine plus oxygen have little effect on cardiovascular dynamics in critically ill patients undergoing open-heart or other major operative procedures, incomplete amnesia and awareness are not infrequent complications of this technique.1 Use of nitrous oxide as a supplement during morphine anesthesia prevents awareness but results in significant cardiovascular depression.2–3 Diazepam and droperidol have also been employed as supplements during morphine anesthesia to prevent awareness. However, the cardiovascular effects of these drugs after large doses of morphine have not been investigated. This study was undertaken to determine the hemo
dynamic effects of two 5-mg doses of diazepam or two 2.5-mg doses of droperidol in patients receiving 1.5–2.3 mg/kg morphine for open
cardiac or major vascular operations.

METHODS

The study was approved by the Human Experimentation Committee of the University of Utah Medical Center. Twenty-nine patients, average age 56 ± 9 (S.D.) years, about to undergo mitral or aortic valve replacement, coronary-artery-vein bypass, or abdominal aortic replacement operations were studied. None was receiving beta-adrenergic receptor blocking drugs, but 16 were taking digitalis preparations. Premedication included morphine (5–10 mg), pentobarbital (60–100 mg), and atropine (0.3–0.5 mg), im, 90 minutes before the scheduled operation. Prior to anesthesia an intravenous line was started in an upper extremity, a central venous pressure catheter was placed percutaneously into the right atrium from the antecubital fossa or neck, and a radial- or brachial-artery catheter was inserted percutaneously and threaded 30–72 cm into the central aorta. The aortic pressure catheter was attached via an arterial pressure transducer to a central digital computer substation in the operating room. Warner’s method of analyzing the central aortic pulse-pressure curve was used to determine cardiac output, stroke volume, arterial blood pressure, and peripheral arterial resistance.4

With the patient breathing 100 per cent oxygen, morphine sulfate was administered intravenously at a rate of 5–15 mg/min. Respirations were first assisted and later controlled to maintain $P_{aO_2}$ as measured in aortic blood every 15–30 minutes, between 30 and 35 mm Hg. A semiclosed circle system provided $CO_2$ absorption and a total fresh gas inflow of 5–6 l/min. When patients became

### TABLE 1. Cardiovascular Effects of Diazepam during Morphine Anesthesia (Mean ± SD)

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<thead>
<tr>
<th></th>
<th>0</th>
<th>After First 5-mg Dose</th>
<th>After Second 5-mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 Min</td>
<td>10 Min</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>96</td>
<td>89±1</td>
<td>89±1</td>
</tr>
<tr>
<td></td>
<td>± 15</td>
<td>± 16</td>
<td>± 14</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.8</td>
<td>4.9</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>± 1.7</td>
<td>± 2.1</td>
<td>± 2.0</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>60</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>± 21</td>
<td>± 20</td>
<td>± 18</td>
</tr>
<tr>
<td>Peripheral resistance (PRU)</td>
<td>159</td>
<td>194±1</td>
<td>185±1</td>
</tr>
<tr>
<td></td>
<td>± 35</td>
<td>± 47</td>
<td>± 38</td>
</tr>
</tbody>
</table>

*P < .05, †P < .025, ‡P < .01, compared with control (0 time) values.
§P < .05 compared with values immediately before the second dose of diazepam.

unresponsive, pancuronium bromide, 0.1 mg/kg iv, was administered and the trachea intubated. Controlled ventilation was initiated using a volume-limited ventilator. Additional pancuronium bromide, 1–3 mg, was administered as necessary. When additional anesthesia was needed, as determined by movement of the patient or increases of blood pressure and pulse rate of 15 per cent or more, additional morphine was given intravenously in 10 mg increments. After each increment of morphine, a 30-minute period of equilibration elapsed before data were collected. Continuous monitoring of the electrocardiogram and recording of arterial and central venous pressures were performed.

Data were obtained before the operation began, after establishing a steady state of anesthesia, and during the operation. Periods chosen for data collection during the operation included those during which surgical stimulation was minimal and consistent. Patients were always ventilated with 100 per cent oxygen and recordings made before and at 5-, 10- and 15-minute intervals after administration of 5 mg diazepam or 2.5 mg droperidol. Following the 15-minute recording a second similar dose of the drug was administered and recordings repeated 5, 10 and 15 minutes later. Data were analyzed for significance using Student's t-test for paired data.

Postoperatively, all patients were questioned with respect to their awareness of the operative procedure.

### RESULTS

Nineteen patients were given diazepam and ten, droperidol, after doses of morphine that averaged 2.0 and 2.1 mg/kg, respectively. Changes in cardiovascular dynamics are given in tables 1 and 2. The initial 5 mg of diazepam resulted in slight but significant decreases, P < 0.025, in heart rate and systolic and mean arterial blood pressures and an increase, P < 0.025, in peripheral vascular resistance. Cardiac output, stroke volume and diastolic blood pressure were also decreased, but the changes were not significant. A second dose of diazepam did not significantly further alter any of the variables except systolic arterial blood pressure, which was further reduced compared with control (pre-diazepam) values, and peripheral arterial resistance, which was further increased compared with control and 15-minute post-diazepam values.

Heart rate and cardiac output were slightly
but significantly increased, $P < 0.05$, and peripheral vascular resistance decreased, $P < 0.05$, 5 minutes after 2.5 mg droperidol. These changes were no longer present 5 or 10 minutes later. All other variables were not significantly altered by droperidol. A second 2.5-mg dose of droperidol produced a transient decrease, $P < 0.05$, and subsequent increase, $P < 0.05$, in peripheral vascular resistance but no significant change in any other variable.

Only one patient in the study, who received droperidol, was aware of any aspect of the operation.

**DISCUSSION**

Diazepam (5–10 mg) and droperidol (5–9 mg) have little effect on cardiovascular dynamics in unanesthetized patients who have cardiac disease.5,8 Diazepam produces slight but significant coronary-artery dilation7 and increases myocardial contractility in dogs.8 As a result of these properties and the well-known amnestic effects of both drugs, they have been advocated as sedative and induction agents for patients who have little cardiac reserve.5,8,9 Both have also been frequently used as supplements during anesthesia with nitrous oxide and fentanyl and, more recently, with morphine and oxygen. However, the effects of diazepam and droperidol on cardiovascular dynamics after large doses of morphine have not been previously reported.

In this study we found that diazepam produced significant but small decreases in arterial blood pressure and heart rate and an increase in peripheral arterial resistance during morphine and oxygen anesthesia. Droperidol, on the other hand, resulted in transient increases in heart rate and cardiac output and a short-lived decrease in peripheral arterial resistance.

These findings are similar to those of Dalen and co-workers5 in unanesthetized patients given 5–10 mg diazepam for cardiac catheterization and Tarhan et al.8 in patients with advanced cardiac disease receiving 5–9 mg droperidol (plus 0.1–0.18 mg fentanyl) for sedation and analgesia for angiography. Our data indicate, therefore, that large doses of morphine do not significantly modify cardiovascular responses to diazepam or droperidol. Since even low concentrations (10–30 per cent) of nitrous oxide produce marked reductions in stroke volume, cardiac output, and arterial blood pressure when added to the inspired mixture of gases of patients anesthetized with morphine and oxygen,5 our

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**TABLE 2. Cardiovascular Effects of Droperidol during Morphine Anesthesia (Mean ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>After First 2.5-mg Dose</th>
<th>After Second 5-mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5 Min</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>99</td>
<td>±14</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.7</td>
<td>±1.0</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>36</td>
<td>±10</td>
</tr>
<tr>
<td>Peripheral resistance (PRU)</td>
<td>217</td>
<td>±39</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113</td>
<td>±19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73</td>
<td>±13</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>92</td>
<td>±15</td>
</tr>
</tbody>
</table>

* $P < 0.05$ compared with control (0 time) values.

§ $P < 0.05$ compared with values immediately before the second dose of droperidol.
findings suggest that diazepam and droperidol may be better supplements than nitrous oxide during morphine anesthesia. Whether diazepam or droperidol produces as much amnesia as nitrous oxide after 2 mg/kg morphine must still be determined. However, the low incidence of intraoperative awareness (1 in 29) in this study is encouraging preliminary evidence that small amounts of either drug may be effective as an amnesic supplement during morphine anesthesia.

REFERENCES


Prolonged Response to Succinylocholine Following Pancuronium Reversal with Pyridostigmine

EDWARD W. BENTZ, M.D.,* AND ROBERT K. STOE尔LING, M.D.†

We recently had a case in which recovery from succinylocholine-induced paralysis was delayed after administration of pyridostigmine to reverse the action of pancuronium.

REPORT OF A CASE

An 82-year-old, 55-kg man who had a six-month history of weight loss (18 kg) was scheduled for an elective exploratory laparotomy. Preoperative laboratory data included hemoglobin 12.5 g/100 ml, total protein 3.9 g/100 ml, albumin 2.0 g/100 ml, creatinine 0.9 mg/100 ml, total bilirubin 21.4 mg/100 ml, direct bilirubin 15.6 mg/100 ml, SGOT 209 units, and alkaline phosphatase 305 units. Serum electrolytes were normal and prothrombin time was 70 per cent. The patient was not taking medications regularly, but received vitamin K preoperatively.

* Anesthesia Resident.
† Associate Professor, Anesthesiology/Pharmacology.

Received from Indiana University School of Medicine, Indianapolis, Indiana 46202. Accepted for publication November 16, 1975.

Address reprint requests to Dr. Bentz.