Hemodynamic Responses to Low Doses of Naloxone after Narcotic–Nitrous Oxide Anesthesia

J. M. Desmonts, M.D.,* G. Bohm, M.D.,† E. Couderc, M.D.†

Hemodynamic responses to reversal of phenoperidine–nitrous oxide anesthesia were studied in 14 adult patients before and after naloxone administration (1.5 ± 0.25 μg/kg), and, at comparable intervals, in 11 control patients who were permitted to resume respiration spontaneously. Naloxone reversal resulted in significant increases in heart rate (31 per cent), cardiac index (50 per cent), left ventricular stroke work index (53 per cent), and systemic blood pressure (21 per cent), compared with initial values. The heart rate–systolic pressure product, an indirect index of myocardial oxygen consumption, increased significantly (77 per cent). However, changes of similar magnitude occurred after spontaneous recovery in control patients, in whom the only significant treatment-related difference was a longer recovery time. Whether naloxone is used or not, the observed hemodynamic changes may be harmful to patients who have diminished cardiac reserve. (Key words: Analgesics, narcotic: phenoperidine. Antagonists, narcotic: naloxone. Heart: myocardial function, narcotics.)

The use of balanced anesthesia, with large doses of narcotic analgesics to supplement hypnotics and muscle relaxants, is increasing. A side effect of this technique is persistent respiratory depression at the end of operation. Rapid reversal of narcotic effect may be accomplished with the antagonist, naloxone, which, as opposed to conventional narcotic antagonists, is devoid of “agonist” actions. However, it has been reported that its use may be associated with tachycardia, arrhythmias, and hypertension.12 These effects may be particularly harmful in patients who have coronary-artery disease.

The aims of the present study were to: 1) examine the cardiovascular effects of narcotic reversal by small titrated doses of naloxone; 2) compare the changes in patients receiving naloxone with those seen after spontaneous recovery in a control group of patients.

Patients and Methods

Twenty-five patients without cardiac or respiratory disease, scheduled for orthopedic or abdominal operations, were studied. Informed consent for these investigations was obtained prior to anesthesia.

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Fourteen patients (Group I) received naloxone at the end of anesthesia and 11 patients (Group II) were allowed to recover spontaneously. Clinical data for the two groups are shown in Table I.

All patients were premedicated with droperidol, 0.2 mg/kg, and atropine, 0 to 10 mg/kg, intramuscularly, 60 min prior to induction of anesthesia. Induction of anesthesia was achieved, in all patients, with sodium thiopental, 3–5 mg/kg, followed by succinylcholine chloride, 1 mg/kg, to facilitate endotracheal intubation. Anesthesia was maintained with nitrous oxide, 60 per cent, and oxygen, 40 per cent. Muscle relaxation was facilitated with pancuronium bromide, 0.05 to 0.08 mg/kg. Each patient received phenoperidine,‡ 1–2 mg, within 20 min of induction and 1 mg every 30 min thereafter, or earlier when clinically warranted (Table I).

Ventilation was controlled throughout anesthesia to maintain arterial carbon dioxide partial pressure (PaCO₂) within a range of 35–40 torr. Blood loss was estimated by weighing sponges and by measuring suction loss and was replaced with lactated Ringer’s solution and packed erythrocytes. Systemic blood pressure was continuously measured with a Statham P 23 db transducer through a percutaneous catheter placed in a radial artery; mean arterial pressure (AP) was obtained directly from an electromanometer (Siemens). The catheter was also used for sampling blood for PaO₂, PaCO₂, and pH determinations. With the aid of continuous electrocardiographic and intravascular pressure monitoring, a no. 7 French triple-lumen Swan-Ganz, flow-directed catheter was placed in the pulmonary artery through an internal jugular vein or antebrachial vein, immediately before or after induction of anesthesia. This catheter was used for measuring pulmonary arterial, pulmonary capillary wedge, and right atrial pressures. Measurements of mean pulmonary arterial pressure (PAP), mean pulmonary capillary wedge pressure (PCWP), and mean right atrial pressure (RAP) were made using Statham P 23 db transducers placed at the level of the right atrium, and were recorded, together with lead II of the ECG, on an MingoGraph 34 (Elemen-
Schonander) four-channel recorder and display oscilloscope. Heart rate (HR) was calculated from the ECG tracing. Cardiac output (CO) was measured by a thermodilution technique. A bolus of 10 ml of 5 per cent dextrose, at 2–5 °C, was injected rapidly into the right atrium. The area under the resulting temperature–time curve was determined by a cardiac output computer (Edwards Cardiac Output Computer, Model 9500). All measurements were performed in triplicate in less than a minute and half, and variation did not exceed 5 per cent; the average value of these three measurements is presented.

From the measured variables, the following data were obtained: pulmonary (PVR) and systemic (SVR) vascular resistances in dynes sec cm⁻⁵:

\[
PVR = \frac{PAP - PCWP}{CO} \times 80
\]

\[
SVR = \frac{AP - RAP}{CO} \times 80
\]

Cardiac index (CI) was calculated by dividing CO by the estimated body surface area and stroke index (SI) by dividing CI by HR. Right (RVSWI) and left (LVSWI) ventricular stroke work indices, in grameters/m², were calculated using the formulas:

\[
RVSWI = 1.36 \frac{(PAP - RAP)}{100} \times SI
\]

\[
LVSWI = 1.36 \frac{(AP - PCWP)}{100} \times SI
\]

The heart rate–systolic arterial pressure product (HR × SAP) was used to evaluate relative changes in myocardial oxygen consumption.

Blood gases and pH were analyzed with standard electrodes at 37 °C and values were corrected to measured body temperature. Esophageal temperature was measured with a thermistor probe. The respiratory rate (RR) was determined clinically, and tidal volume was measured with a Wright respirometer.

In both groups of patients, the first set of measurements was made at the end of the surgical procedure. Neuromuscular function was evaluated clinically, and neostigmine was not needed for any patient. The patients were allowed to breathe 100 per cent oxygen spontaneously or, when respirations were absent, ventilation was maintained by gently compressing the reservoir bag. The following data were recorded: HR, AP, PAP, PCWP, CO, CI, SI, RAP, SVR, PVR, RVSWI, LVSWI, RR, PetO₂, and pH. After completion of these measurements, Group I patients received naloxone, 1 µg/kg, intravenously, every 3 min until the spontaneous respiratory rate reached 12/min and the tidal volume 8 ml/kg. When these values were achieved, the tracheas were extubated. The second set of measurements was made 5 min after extubation. Group II patients did not receive naloxone; rather, the tracheas were extubated when they could open their eyes on command, when the respiratory rate had reached at least 12/min and the tidal volume 8 ml/kg. Five minutes after extubation a second set of measurements was made in this group. To determine the significance of observed changes, intragroup comparisons between the first and second sets of measurements were made employing Student's t test for paired data. To determine whether the two types

### Table 1. Clinical Data (Mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Group I Naloxone (n = 14)</th>
<th>Group II Control (n = 11)</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>55 ± 4</td>
<td>58 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>39, 116</td>
<td>69, 56</td>
<td>—</td>
</tr>
<tr>
<td>Type of operation</td>
<td>Orthopaedic 8</td>
<td>Orthopaedic 6</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Abdominal 6</td>
<td>Abdominal 3</td>
<td>—</td>
</tr>
<tr>
<td>Amount of phenoperidine (µg/kg)</td>
<td>33.3 ± 4</td>
<td>26.9 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Delay between last injection of phenoperidine and end of operation (min)</td>
<td>55 ± 8</td>
<td>61 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Time between the end of operation and extubation (min)</td>
<td>5 ± 0.3</td>
<td>21 ± 6</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Naloxone, µg/kg</td>
<td>1.5 ± 0.25</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Group I vs. Group II. NS = not significant.

### Table 2. Respiratory Rate and Blood-gas Data (Mean ± SE) before and after Recovery

<table>
<thead>
<tr>
<th></th>
<th>Before Recovery</th>
<th>After Recovery</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I Naloxone (n = 14)</td>
<td>Group II Control (n = 11)</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (l/min)</td>
<td>4 ± 1</td>
<td>6 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>48 ± 1.9</td>
<td>51 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂ (torr)</td>
<td>7.31 ± 0.02</td>
<td>7.24 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7.37 ± 0.05</td>
<td>7.27 ± 0.01</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

* Group I vs. Group II. NS = not significant.
of recovery differed, postanesthetic data for the two groups were compared by means of Student's t test for unpaired data. Statistical significance was defined as $P \leq 0.05$. Data are means ± standard errors (SE).

**Results**

The homogeneity of the two groups was assessed by statistical comparison of the data in table 1. Only the times from the end of operation to extubation were significantly different, being shorter in the group treated with naloxone. Titration of naloxone according to respiratory rate resulted in the use of a very small total dose, 1.5 ± 0.25 μg/kg. Most patients needed only one injection, and there was no recurrence of respiratory depression later in the recovery room. Following administration of naloxone, the respiratory rate increased from 4 ± 1 to 15 ± 1/min, along with a decrease in $P_{\text{aCO}}$, from 48 ± 2 to 43 ± 1 torr. In control patients, recovery from respiratory depression required more time but, after extubation, only $P_{\text{aCO}}$ was significantly different from that observed in patients treated with naloxone (table 2). Since all patients were breathing 100 per cent oxygen, $P_{\text{aO}}$ exceeded 100 torr in every case.

Initial hemodynamic values for the two groups are shown in table 3. After administration of naloxone, significant increases were observed in the following variables: HR (+31 per cent), CI (+50 per cent), LVSWI (+53 per cent), AP (+21 per cent) and HR × SAP (+77 per cent). SVR decreased significantly (-13 per cent), while no significant change was present in PAP, PVR or RVSWI. These changes are represented in figures 1 and 2. The average percentage changes in hemodynamic variables following spontaneous recovery were similar to those observed in patients treated with naloxone. As in Group 1, significant differences were present in control patients for HR, CI, LVSWI, and AP and HR × SAP.
Intergroup comparisons of hemodynamic data generally showed no difference except that PVR was lower in Group 1, both before and after naloxone treatment.

**Discussion**

Recovery from general anesthesia is associated with increased autonomic nervous system discharge, with the pattern dependent upon the anesthetic and adjuvant drugs. Hemodynamic features in patients without heart disease are increases of heart rate, arterial pressure, cardiac output, and systemic vascular resistance. The factors responsible for this sympathetic stimulation include postoperative pain, hypercapnia, hypoxia, emergence excitement, and moderate hypothermia. Hypercapnia, related to narcotic-induced respiratory depression, can be rapidly reversed by the administration of naloxone. Reversal, however, may also result in loss of analgesia. The sudden appearance of pain is associated with cardiovascular effects similar to those seen after the abrupt withdrawal of narcotics in addicts. Adequate analgesia during the postoperative period can be preserved by judicious titration of naloxone dosage.

Data from animal experiments suggest large changes in hemodynamic variables following the administration of naloxone after narcotics. Freye reported increases of heart rate, arterial pressure and left ventricular dP/dt, to as much as 100 per cent above control values. However, the naloxone dosage in this experiment was very large, 0.4 mg/kg, quite different from that used clinically. In non-narcotized dogs, large doses of naloxone produced no cardiovascular effect. It is likely, therefore, that naloxone itself does not cause cardiovascular changes in patients. Recent data of Patschke et al. demonstrated stimulation of the cardiovascular system with a more moderate dose of naloxone, 15 μg/kg. The most marked effect was an increase in heart rate of 73 per cent, resulting in a smaller increase (20 per cent) in cardiac output. Blood pressure increased by 20 per cent and systemic vascular resistance remained unaffected. These changes led to an increase in myocardial oxygen consumption of approximately 66 per cent. The results of clinical study in neurosurgical patients are in accordance with animal data. Two groups of patients were studied, one receiving 0.1 and the other 0.4 mg naloxone. Marked cardiovascular effects were seen with the large dose; however, comparison with a control group was lacking.

The present controlled study was carried out to determine the effects of abrupt reversal of narcotics with naloxone at the end of anesthesia. Naloxone was administered in increments of 1 μg/kg, in order to achieve a respiratory rate of 12/min. Only a small dose, 1.5 ± 0.25 μg/kg, was needed. The cardiovascular effects were similar to those previously reported, and also, not different from those observed after spontaneous recovery. Spontaneous recovery, however, was less rapid than naloxone-induced reversal, and perhaps permitted a more gradual adaptation of cardiac performance to the demands of the awake state. The similarity to spontaneous recovery suggests that these effects are related to stress and pain, rather, than to specific interaction between narcotics and naloxone. Such interaction was proposed by Freye, who suggested that there was competition for central nervous system receptor sites by these drugs. Whatever the mechanism, the cardiovascular responses of recovery, demonstrated in the present study, may not be well tolerated by patients who have coronary-artery disease, so that additional drug therapy may be required in the early postoperative period. Narcotics may be administered, in which case there may be a need for prolonged mechanical ventilation. Prys-Roberts et al. have proposed prophylactic beta-adrenergic receptor blockade in cardiac and hypertensive patients to attenuate the cardiovascular responses of postoperative stress.
Several conclusions emerge from this study. First, narcotic reversal by judicious titration of even small doses of naloxone is, nevertheless, followed immediately by marked hemodynamic responses. Second, the changes are not significantly different from those observed with spontaneous recovery, although the onset of the latter occurs later. These changes may be harmful to patients who have diminished cardiac reserve.

The authors gratefully acknowledge the expert assistance provided by Dr. R. I. Maze in the preparation of this manuscript. Naloxone HCl (Narcan) was supplied by Endo Laboratories, Inc.

References