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## High-dose Fentanyl for Neuroanesthesia

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High-dose fentanyl-oxygen anesthesia (HDF), well-established in cardiac surgery,<sup>1</sup> may offer several advantages to the neurosurgical patient. Cardiovascular stability characteristic of this technique would be desirable in neuroanesthesia where hypotension may reduce cerebral blood flow in a brain with poor autoregulation while hypertension may induce vasogenic edema. Since specific antagonists are available, HDF can be reversed in the postoperative period without eliminating its postoperative analgesic effect.<sup>2</sup> Thus, careful neurologic monitoring to detect complications of surgery in the postoperative period would be feasible. For procedures in the sitting position, omission of nitrous oxide should reduce the severity of venous air embolism.<sup>3</sup> We have employed HDF with postoperative naloxone administration in neurosurgical anesthesia.

### MATERIALS AND METHODS

This study was approved by the Human Studies Committee of Temple University Hospital. Informed consent was obtained from each patient.

Ten patients without organic heart disease and 35 to 65 years of age were studied. All were scheduled for suboccipital craniectomies in the sitting position for tumor removal or microvascular cranial nerve decompression. The mean length of operation was 262 min (90-360 min). Premedication was 5 to 10 mg diazepam, po, and 0.4 mg atropine, im, 1.5 h prior to induction of anesthesia. After application of the ECG and insertion of a peripheral venous cannula in the operating room, a radial artery catheter was inserted to monitor arterial blood pressure (MAP) and arterial blood gases (ABG). A precordial bubble doppler was positioned and a thermodilution balloon-tipped catheter was inserted into the pulmonary artery to measure changes in pulmonary artery pressure (MPAP) and cardiac output (CO) for the detection and removal of entrained venous air.<sup>4</sup> The magnitude of neuromuscular blockade was monitored using train-of-four (TOF) stimulation of the ulnar nerve. Temperature, urine output, expired CO<sub>2</sub> levels, and a two-lead EEG also were monitored during the procedure.

After a period of stabilization and measurement of baseline values, fentanyl was infused at a rate of 150

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TABLE 1. Cardiovascular Responses during High-dose Fentanyl-O<sub>2</sub> Neuroanesthesia and Operation\*

	Preinduction	Intubation	Intubation + 5 min	Head Pins	Sitting	Sitting + 5 min	Incision	Incision + 5 min	Craniectomy	End Surgery
Heart rate (beats/min)	97 ± 6	102 ± 7	102 ± 7	92 ± 5	93 ± 6	84 ± 5	82 ± 7	85 ± 7	82 ± 4	88 ± 5
Mean arterial pressure (mmHg)	96 ± 5	97 ± 6	100 ± 6	97 ± 8	92 ± 8	93 ± 6	72 ± 6†	74 ± 8†	83 ± 5	81 ± 4†
Cardiac output (liters/min)	7.4 ± 1.1	6.3 ± 1.1†	6.2 ± 0.9	NA	5.1 ± 0.7†	4.8 ± 0.6	5.1 ± 0.6†	4.8 ± 0.5†	4.1 ± 0.6†	5.7 ± 1.3†
Mean pulmonary artery pressure (mmHg)	13 ± 3	11 ± 3	13 ± 4	NA	9 ± 3	8 ± 3	10 ± 3	9 ± 2	8 ± 2	7 ± 2

\* Mean values ± SEM.

†  $P < 0.05$ . Student's paired  $t$  test when compared with preinduction values.

μg/min and oxygen breathed spontaneously via a mask. Ventilation was assisted and verbal contact with the patient was maintained until loss of consciousness. After three minutes, 0.18 mg/kg *d*-tubocurarine and 0.02 mg/kg pancuronium were given iv to provide paralysis with minimal alterations in cardiovascular hemodynamics.<sup>5</sup> In addition, 0.4 mg scopolamine was given iv and the rate of the fentanyl infusion was increased to 250 μg/min until 100 μg/kg had been given. The trachea was intubated after infusion of 20 μg/kg fentanyl, iv, and ventilation controlled to maintain PaCO<sub>2</sub> near 30 mmHg intraoperatively. For hypertension thought to be caused by light anesthesia, fentanyl was administered in 250-μg increments when systolic pressure increased more than 20% above preinduction values. MAP, HR, MPAP, and CO were measured during endotracheal intubation, application of head pins (excluding MPAP and CO), the change to sitting position, incision, craniectomy, and at the end of surgery. Abolition of the fourth twitch (TOF) was maintained with increments of 0.2 mg/kg pancuronium. A single dose of 20 mg furosemide was administered iv during craniectomy. After completion of surgery, 2 mg/kg thiopental, iv, were given before manipulation of the head and reversal of paralysis with neostigmine and atropine.

In the immediate postoperative period following transport to the neurosurgical intensive care unit, all patients received a bolus iv injection of 1.5 μg/kg naloxone, repeated if necessary until awake, and followed by a continuous infusion at a rate of 6–12 μg/min to maintain respiratory rate (RR) greater than 12 breaths/min. MAP, HR, ABG, RR, and Glasgow Coma Score (GCS) were recorded at 30-min intervals. Time from arrival in intensive care to extubation of the trachea also was measured. The incidence of nausea, vomiting, and headache was recorded by ancillary medical personnel. Patients also were interviewed by the anesthetist one day postoperatively to assess their memory of induction of anesthesia and surgery.

Data were analyzed using analysis of the variance and Student's paired  $t$  tests. Significance was defined as  $P < 0.05$ .

## RESULTS

Cardiovascular responses during HDF and operation are presented in table 1. No increases in MAP, MPAP, HR, and CO were observed during the induction of anesthesia and intraoperative course. A decrease in MAP occurred at incision after infiltration of the scalp with 0.5% lidocaine and epinephrine 1:200,000 and at end surgery. CO declined after loss of consciousness and remained lower than the preinduction value. An 18 to 23% decrease in CO was observed upon the change to the sitting position.

No chest wall rigidity was observed during induction of anesthesia before administration of muscle relaxations in any patient. EEG spikes were observed in two patients approximately one hour following termination of the fentanyl infusion. Entrained venous air was detected in two patients, one of whom exhibited an increase in MPAP and a decrease in MAP. Small bubbles of air were aspirated easily from the proximal port of the pulmonary artery catheter for several minutes. The monitored hemodynamic variables returned to within normal limits and elimination of detectable air in both cases followed careful inspection of the wound for bleeding and packing with wet dressings.

Postoperatively, time to tracheal extubation was 22 ± 13 minutes (mean value ± SD). Responses during continuous naloxone infusion are presented in table 2. The total dose of naloxone, administered for an average duration of 18 hours, was 6,775 ± 3,591 μg (mean value ± SD). No changes in MAP and HR were observed when compared with preinduction values. RR was maintained at 12 to 20 breaths/min, and GCS was greater than 12 throughout the postoperative course. Headache and nausea, which was treated with small doses of pro-

TABLE 2. Postoperative Responses\* during Continuous Naloxone Infusion† after High-dose Fentanyl-O<sub>2</sub> Neuroanesthesia

	Time in Hours After Arrival in Intensive Care								
	0.5	1	2	3	4	6	8	10	12
Heart rate (beats/min)	99 ± 2	94 ± 3	97 ± 4	90 ± 4	93 ± 3	94 ± 3	94 ± 3	91 ± 3	92 ± 3
Mean arterial pressure (mmHg)	90 ± 6	87 ± 7	83 ± 6	89 ± 6	87 ± 6	89 ± 5	90 ± 5	91 ± 4	90 ± 6
Respiratory rate (breaths/min)	17 ± 1	17 ± 1	17 ± 2	18 ± 1	17 ± 1	17 ± 1	18 ± 1	18 ± 1	18 ± 6
Glasgow Coma Score (max = 15)	12 ± 1	13 ± 1	13 ± 1	13 ± 1	14 ± 1	14 ± 1	14 ± 0	14 ± 1	14 ± 1

\* Mean values ± SEM.

† Total dose of naloxone given + 6,775 ± 359 µg (Mean ± SD).

chlorperazine, occurred in four and five patients, respectively. No patient had any memory of the anesthetic induction or tracheal intubation. One patient who had microvascular decompression surgery recalled an electric shock during stimulation of the cranial nerve. One death occurred five days after removal of an acoustic neuroma. Recovery in the intensive care unit had been satisfactory except for a unilateral depression of the gag reflex due to surgical manipulation of the brainstem. The apparent cause of death was pulmonary aspiration of gastric contents followed by respiratory arrest and not attributable to the anesthetic management.

#### DISCUSSION

HDF (100 µg/kg) for neurosurgery prevented increases in blood pressure and heart rate during endotracheal intubation, incision, and craniectomy. The decrease in CO observed during assumption of the sitting position was similar to that reported by others.<sup>6</sup> Following infiltration of the scalp, systemically absorbed epinephrine mediated beta-adrenergic peripheral vasodilatation. This resulted in the decrease in MAP observed at the time of incision, since MAP did not change in subsequent cases where epinephrine was omitted. The decrease in MAP observed at the end of surgery was probably a result of the administration of thiopental, which was included as a modification of the technique after two cases of abrupt awakening early in the series occurred at the end of surgery.

Chest wall rigidity which has been described with HDF<sup>7</sup> was not observed in this study, since the infusion rate of fentanyl was not greater than 250 µg/min during the induction of anesthesia and muscle relaxants were given immediately following loss of consciousness. The incidence of venous air embolism observed in this investigation was similar to that reported previously in neurosurgical patients who received nitrous oxide as

part of their anesthetic management.<sup>8</sup> Therefore, the results of our study do not establish that elimination of nitrous oxide decreases the incidence of air embolism.

In rats which have an ED<sub>50</sub> for fentanyl analgesia similar to humans, large doses of fentanyl (200 to 400 µg/kg) induce seizures.<sup>9</sup> EEG spikes were observed in two patients in this study more than one hour after infusion of 100 µg/kg fentanyl. They did not appear as frequently or at the same time as sharp waves reported in the EEGs of cardiac surgical patients receiving HDF and premedicated with lorazepam.<sup>10</sup> Brain concentrations of fentanyl have been shown to decrease more gradually than plasma concentrations after rapid injection of fentanyl in rabbits.<sup>11</sup> In addition, moderate hyperventilation of patients may have been responsible for the late occurrence of EEG spikes in this study, since brain concentrations of fentanyl peaked higher and later in dogs who were hyperventilated and given fentanyl.<sup>12</sup>

Isolated case reports of severe hypertension, paroxysmal atrial tachycardia, ventricular arrhythmias, and acute pulmonary edema secondary to naloxone administration for reversal of narcotic anesthesia have been reported.<sup>13-15</sup> Naloxone, 0.1 to 0.4 mg, iv, was given to patients already receiving various combinations of antiarrhythmics, inotropes, and vasodilators in the postoperative period after high-dose morphine-nitrous oxide anesthesia for cardiothoracic procedures. Following these initial reports, none of which can be considered clear evidence of adverse cardiovascular effects of naloxone, several clinical reports surfaced in which bolus injections of 0.4 mg of naloxone were alleged to have caused undesirable pressor responses, rupture of a cerebral aneurysm, and sudden death.<sup>16-18</sup> These reports clearly indicate a need for caution in administering naloxone following narcotic anesthesia. Cardiovascular status should be monitored during naloxone administration. In addition, bolus iv injections of naloxone should

not exceed 1 to 1.5  $\mu\text{g}/\text{kg}$  and probably should be avoided in patients with uncontrolled hypertension or marginal cardiac reserve concurrently receiving sympathomimetic therapy.

Previous investigators<sup>19,20</sup> reported no adverse cardiovascular effects during reversal of EEG and respiratory depressant effects of high-dose morphine anesthesia with an intravenous naloxone infusion. In this investigation careful infusion of naloxone maintained stable cardiovascular hemodynamics, a satisfactory level of consciousness, and prevented respiratory depression in the postoperative period. Although four of the neurosurgical patients in this study developed headache, the level of analgesia was felt by the patients and the investigators to be acceptable.

In summary, HDF followed by postoperative naloxone administration provided satisfactory anesthesia and reliable reversibility without impairment of cardiovascular status in ten neurosurgical patients. Although it was not compared with other accepted neuroanesthetic methods, this technique was found to be readily applicable to neurosurgery in the sitting position.

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