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Delayed Respiratory Depression after Alfentanil

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Delayed respiratory depression following narcotic administration has been reported by several authors.[1,2] The new synthetic short-acting narcotic, alfentanil, was developed to facilitate rapid recovery of respiratory and psychomotor function following general anesthesia. We report two cases of delayed respiratory depression occurring following administration of alfentanil.

CASE REPORTS

Case 1. A 19-yr-old, 80-kg man with progressive idiopathic kyphoscoliosis presented to the operating room for removal of Harrington Rods and repeat posterior spinal fusion from T2–L1 with Cotrell-Dubousset instrumentation. The procedure was being performed because the patient had developed painful pseudoarthorses and worsening scoliosis (50° thoracic curve). The patient's medical history was otherwise negative, and he had a normal exercise tolerance. Physical examination was unremarkable except for scoliosis. Laboratory values including pulmonary function tests were within normal limits. No premedication was given. Monitoring with EKG, automated blood pressure cuff, pulse oximeter, and precordial stethoscope was established. Anesthesia was induced with alfentanil, 75 μg/kg; thiopental, 1 mg/kg; and atracurium, 0.5 mg/kg, iv. After placement of an arterial line for sampling of blood gases, the patient was placed in the prone position. Anesthesia was maintained with a 1.0–1.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil infusion, and 70% nitrous oxide. Arterial blood pressure was maintained at a mean of 70–75 mmHg. This was facilitated with incremental iv doses of labetalol (total dose 20 mg). The alfentanil infusion was adjusted continuously to the minimum dose compatible with acceptable vital signs. The infusion could not be reduced below 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without producing hypertension and tachycardia despite treatment with labelalol. Somatosensory evoked potentials did not change during the course of surgery. An intraoperative wake-up test was performed with prompt (<2 min), smooth awakening. Anesthesia was reinduced with thiopental, 50 mg iv, and inhalation of 70% nitrous oxide. The alfentanil infusion was discontinued 20 min prior to the end of the case. Total infusion time was 465 min, and the total alfentanil dose including boluses was 55 mg or an average of 1.48 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over the case. At the end of surgery, the patient awakened 2 min after the nitrous oxide was discontinued. No muscle relaxation had been given for the last 4 h, and the patient had both a sustained tetanic response to 100 hz stimulation for 5 s and a normal grip strength. No anticholinesterase was given. After documentation of a normal neurologic examination and an end-tidal P_{CO_2} of 38 mmHg with the patient breathing spontaneously, the trachea was extubated. On arrival in the recovery room, the patient was noted to be breathing spontaneously, awake, and alert. Vital signs included an arterial blood pressure of 110/60 mmHg, a heart rate of 86 bpm, a respiratory rate of 12 breaths/min, and an oral temperature of 35.8° C. The patient's vital signs recorded every 5 min remained stable with no record of respiratory rate below 10 breaths per minute or depressed mental status until 25 min after arrival in the recovery room (45 min after discontinuing the alfentanil infusion). At that time, the patient was found unresponsive and apneic. Vital signs included an arterial blood pressure of 190/100 and a heart rate of 55 bpm. The patient was not cyanotic but had severely miotic pupils. Mask ventilation was instituted without difficulty. Analysis of arterial blood gases revealed pH_a = 7.10, Pa_{O_2} = 338 mmHg, and Pa_{CO_2} = 70 mmHg. The trachea was intubated and controlled ventilation instituted. The patient continued to show a sustained response to tetanic stimulation as delivered by a peripheral nerve stimulator. Ten minutes later, the hypercarbia had resolved (pH_a = 7.32, Pa_{O_2} = 560 mmHg, Pa_{CO_2} = 41 mmHg), but the patient continued to be unresponsive with miotic pupils. Naloxone was given in 40 μg increments to a total of 120 μg, iv. Level of consciousness increased slowly over 10 min to the point where the patient would follow simple commands. Neurologic evaluation revealed no focal deficits. The patient became gradually more alert during the next 2 h, and his trachea was extubated. Subsequent arterial blood gases documented normal oxygenation and ventilation. The morning following surgery, the patient was awake and alert, and the mental status examination was unchanged from the preoperative examination.

Case 2. A 13-yr-old, 46-kg man with progressive idiopathic scoliosis presented to the operating room for a T4–L1 posterior spinal fusion with Cotrell-Dubousset instrumentation and left thoracoplasty. Past medical history was unremarkable except for a premature birth at 7 months gestational age with subsequent normal growth and development. Exercise tolerance was normal. Physical examination was unremarkable except for scoliosis (50° thoracic curve). Laboratory values including pulmonary function studies were within normal limits. No premedication was given. Monitoring with EKG, automated blood pressure cuff, pulse oximeter, and precordial stethoscope was established. Anesthesia was induced with alfentanil, 75 μg/kg; thiopental, 4 mg/kg; and vecuronium, 0.2 mg/kg, iv. Anesthesia was maintained with an alfentanil infusion 1.5–1.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 70% nitrous oxide,

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and incremental iv doses of vecuronium. After placement of an arterial catheter and a central venous pressure line, the patient was placed in the prone position. Mean arterial blood pressure was maintained between 70 and 80 mmHg with a total of 1 mg/kg labetalol and an iv nitroglycerine infusion as needed. The alfentanil infusion was adjusted according to the patient's vital signs and could not be reduced below 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without producing excessive hypertension and tachycardia despite iv nitroglycerine and labetalol. Somatosensory evoked potentials did not change during surgery. An intraoperative wake-up test was performed with rapid awakening after discontinuing nitrous oxide. Anesthesia was reinduced with thiopental, 50 mg iv, and inhalation of nitrous oxide. The alfentanil infusion was discontinued 20 min prior to the end of the case. The duration of the alfentanil infusion was 330 min, and the total alfentanil dose was 24 mg or an average of 1.58 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over the entire case. At the completion of the case, the patient awakened 2 min after nitrous oxide was discontinued. Since no vecuronium had been given for more than 2 h and the patient had both a sustained response to 100 hz tetanic stimulation and a normal grip strength, no anticholinesterase was given. After documentation of a normal neurologic examination and maintenance of an end-tidal CO_2 of 30 mmHg with spontaneous respirations, the trachea was extubated. He was transported to the surgical intensive care unit where, on arrival, arterial blood pressure was 130/80 mmHg, heart rate 56 bpm, and respiratory rate 10 breaths/min. His temperature was less than 35° C orally. He was fully alert and conversed spontaneously. The patient's vital signs, recorded every 5 min, were normal until 20 min after arrival in the surgical intensive care unit (approximately 45 min after the alfentanil infusion was discontinued). At that time, the patient was noted to be unresponsive and apneic. Vital signs included an arterial blood pressure of 200/100 mmHg and a heart rate of 25 bpm. The patient was mildly cyanotic and showed severely miotic pupils. Atropine, 1 mg iv, was given and ventilation *via* a mask was attempted. Ventilation was extremely difficult because of marked truncal rigidity. Succinylcholine 80 mg was given iv, and ventilation *via* a mask was successfully initiated. The trachea was intubated and ventilation controlled. Arterial blood gas analysis revealed pH_a = 7.06, Pa_{O_2} = 462 mmHg, and Pa_{CO_2} = 90 mmHg. Blood was drawn for determination of alfentanil concentration at that time (serum removed immediately and frozen at −70° C) and sent for analysis. Within 10 min of intubation, the patient was awake, alert, and following all commands. Control twitch height was attained 15 min after administration of succinylcholine. However, the trachea was kept intubated for the next 24 h because of elevated Pa_{CO_2} values (morphine was given for pain during this period). He was subsequently discharged from the intensive care unit without neurologic sequellae. The blood alfentanil concentration at the time of the respiratory arrest was reported several weeks later to be 87 ng/ml by radioimmunoassay.

Discussion

These two patients demonstrated delayed, life-threatening respiratory depression following prolonged infusion of the short-acting narcotic, alfentanil. While this phenomenon is described following intraoperative fentanyl administration,[1,2] it has not been previously reported with alfentanil.

Several human studies have been performed both to document and explain delayed respiratory depression following fentanyl administration. Becker *et al.*[2] examined CO_2 response curves in 29 surgical patients who received small doses of fentanyl intraoperatively. Twenty-six of these patients showed evidence of delayed respiratory depression. This delayed respiratory depression could not, however, be confirmed in a similar study by Smedstad.[3] A study by Stoeckel *et al.* involving ten patients established a relationship between an observed delayed respiratory depression and a delayed increase in plasma fentanyl levels.[4] Since delayed respiratory depression following alfentanil has not been previously reported, similar studies have not been performed. However, in a study specifically examining CO_2 response curves after alfentanil administration, there was no evidence of delayed respiratory depression.[5]

Both of these patients received doses of alfentanil well within the prescribed dosage range for general surgical cases.[6] The alfentanil infusion rate was titrated to level of surgical stimulus, and the infusions were discontinued at an appropriate time. Both individuals were awake and alert enough to undergo complete motor and sensory neurologic examinations at the end of the case. They also exhibited a normal end-tidal P_{CO_2} level at the end of the case. The severe respiratory depression was noted 45 min after the infusion had been discontinued in both cases. However, significant respiratory depression began earlier than that time as is evidenced by the severely elevated Pa_{CO_2} values that were obtained in each case after ventilation *via* a mask had begun. The second patient had a plasma alfentanil level of 87 ng/ml at the time of his respiratory arrest. This level is below the level where spontaneous ventilation normally resumes (99–240 ng/ml).[6] The alfentanil level at the onset of the respiratory depression may, however, have been higher. In addition, patients show variability in sensitivity to narcotics, and thus a single plasma alfentanil level in an individual patient may not be a good predictor of response. Also, since hypothermia decreases the slope of the CO_2 response curve, decreased core temperature in both of these patients could have played a role in the development of respiratory depression.

The fact that both of these patients had idiopathic scoliosis raises the question as to whether this type of patient is inordinately sensitive to narcotics. Some patients with secondary scoliosis (*e.g.*, neuromuscular diseases) are thought to be abnormally sensitive to narcotics,[7] but there are no reports of increased narcotic sensitivity in patients with idiopathic scoliosis. However, the slope of the CO_2 response curve in patients with scoliosis has been shown to be reduced preoperatively to a degree proportional to the reduction in vital capacity.[8] There are no studies examining CO_2 response curves in postoperative scoliosis patients.

Another important factor in the development of postoperative respiratory depression is the level of stimulation given to the patient. Sleep causes displacement of the CO_2 response curve to the right.[9] Thus, a patient in the re-

covery room who is constantly stimulated by the nursing staff and remains awake will show less respiratory depression than the patient who is not stimulated and falls asleep.

A final consideration in these patients would be an adverse drug interaction resulting in either increased respiratory depression or in prolongation of the action of alfentanil. Neither of these patients received any anesthetic medications other than alfentanil, nitrous oxide, relaxant, and thiopental. In this group of drugs, only alfentanil, thiopental, and the muscle relaxants have significant respiratory depressant properties. Since neither patient had received more than 1 mg/kg of thiopental during the last hour of the case or more than 5 mg/kg for the entire case, respiratory depression from thiopental is unlikely. Also, neither patient showed any evidence of residual neuromuscular blockade. Drug interactions between alfentanil and the antihypertensive medications, labetalol and nitroglycerine, have not been previously reported. Whether these drugs played a role in these cases is unknown, but such an interaction is highly unlikely.

Clinically, both of these patients exhibited delayed respiratory depression similar to that observed in some patients after fentanyl administration. The rigidity observed in the second patient has also been observed in patients with postoperative respiratory depression following fentanyl.[10] The clinician should be aware that delayed respiratory depression may occur when alfentanil infusions are used for long cases. The fact that alfentanil is a short-acting drug should not lure the clinician into omitting close respiratory monitoring and appropriate patient stimulation during the recovery period.

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Atrial Esophageal Pacing in Patients Undergoing Coronary Artery Bypass Grafting: Effect of Previous Cardiac Operations and Body Surface Area

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Atrial esophageal pacing is a fast, easy, relatively benign method of cardiac pacing. In patients with bradycardia, pacing increases cardiac output and raises coronary perfusion pressure,[1] and, therefore, may be useful in patients at risk of developing bradycardia and ischemia intraoperatively. This is especially true in patients undergoing coronary artery bypass grafting secondary to their underlying disease and the drugs they commonly receive, namely beta adrenergic blockers and calcium channel entry blockers. Induction of anesthesia, especially with high-dose opioids and post-tracheal intubation, is frequently attended by bradycardia.

The factors limiting use of esophageal pacing include pacing current threshold levels, inability to consistently pace the ventricle, inadvertent diaphragmatic pacing, and the potential for esophageal injury. The mechanical as-

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