Anaphylactic Reaction to Epidural Fentanyl

BARBARA ZUCKER-PINCHOFF, M.D.,* SIVAM RAMANATHAN, M.D.†

Hypersensitivity to fentanyl is extremely rare. An anaphylactic reaction to an epidurally administered drug has also seldom been reported. This paper presents a personal experience of generalized erythema, edema, and vascular collapse associated with the administration of epidural fentanyl. It is written from the point of view of the first author who was also the patient. The second author was the anesthesiologist. Hypersensitivity to fentanyl was later confirmed by intradermal testing. Results of intradermal testing with related opioids and the antagonist naloxyne are also presented.

CASE REPORT

I presented as a 35-yr-old, gravida 2, para 1 female at term for repeat cesarean section. Past medical history was unremarkable except for an allergy to IVP dye that caused itching and hives as well as a history of hay fever occasionally accompanied by mild wheezing. Twenty years ago the hay fever resulted in severe bronchospasm requiring a single injection of epinephrine. Past surgical history included a tonsillectomy at age 14 and a cesarean section 3 yr ago. Anesthesia for the first cesarean consisted of epidural bupivacaine, supplemented intravenously with fentanyl 50 μg and droperidol 2.5 mg. I also received 5 mg of epidural morphine in the recovery room. The peroperative course was uneventful.

For the cesarean being presented, no premedication was given. A 16-G catheter was inserted intravenously, and a catheter was introduced into the epidural space via the L2-5 interspace. After hydration with 1000 ml of lactated Ringer's solution, a T10 level of anesthesia was achieved using 10 ml of preservative-free lidocaine 2% with epinephrine 1:200,000. Due to a surgical delay, I was brought to the operating room 1 h later. With a wedge in place to maintain left uterine displacement, a T4 sensory level of anesthesia was induced using 10 ml of the same local anesthetic, while an additional 1000 ml of lactated Ringer's was infused. Three boluses of ephedrine, 5 mg, were required to maintain systolic blood pressure above 100 mmHg.

Ten minutes into the procedure, 2 ml of 50 μg/ml fentanyl were injected into the epidural catheter. Within 10 min of the injection, I complained of itchy eyes, followed by nasal congestion, and then a warm face. The sensation was exactly the same as an allergic reaction to an environmental allergen. I thought I was allergic to something in the air conditioning! It never occurred to me that I was experiencing anaphylaxis. Injected conjunctivae, and erythema and edema of my face and hands were noted. Two doses of diphenhydramine 50 mg iv produced no improvement. The blood pressure declined to 70/40 and did not increase with ephedrine 10 mg. By this time I was quite groggy, whether from the diphenhydramine or hypotension is uncertain. Profuse bleeding was noted in the surgical field and a second 16-G iv catheter was inserted. When the second iv was started, I remember thinking "This must be serious." Albumin 5% 500 ml and 1000 ml of lactated Ringer's were rapidly infused. Epinephrine 100 μg iv restored the blood pressure. As I heard the discussion of whether or not to give epinephrine, I kept thinking "I'm so glad I'm not taking care of me!" Erythema and edema of the hands and face also began to resolve. During this time a vigorous baby girl, Apgar scores 8 and 9, was delivered. After the initial response to the epinephrine bolus, erythema and edema of the hands and face recurred, requiring epinephrine boluses every 15 min. It was fascinating to feel my hands gradually swell, become stiff, and my wedding ring get tight. With a bolus of epinephrine, I could feel an occasional PVC (and watch it on the EKG monitor), could feel my hands and face cooling and my fingers loosening up. Methyl prednisolone, 500 mg, was given iv. In the recovery room, an epinephrine infusion was used at a rate of 0.2 μg/min, and decreased gradually over 3 h. One hour after delivery, epidural morphine 5 mg was given via the epidural catheter without complication. A second dose of epidural morphine was safely administered 24 h later.

Seven months after the events described, skin testing was performed comparing reactions of an individual with no known allergies and myself. For all skin testing, 0.9% saline was used as a negative control, and d-tub curare as a positive control. A volume of 0.25 ml of each solution was injected intradermally. Responses were measured 15 min after injection. Results are summarized in table 1.

Six months after the initial intradermal testing, I was further investigated. Injections of 0.05 ml of each solution were made intradermally, and the responses read 15 min later. This set of tests was performed twice, once on my forearms and once on my back, each with the same results as summarized in table 2.

DISCUSSION

Pinpointing the source of an adverse drug reaction can be a complex task when multiple drugs are given over a short period of time, sometimes via different routes of administration. This case was unusual. In the 30 min preceding the onset of signs and symptoms of anaphylaxis, only epidural fentanyl was administered. The subsequent positive skin testing supports the diagnosis of fentanyl hypersensitivity.

In the literature, only one report of a possible anaphylactic reaction following epidural drug administration


* Instructor.
† Professor.
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Address reprint requests to Dr. Zucker-Pinchoff.
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TABLE 1. Responses to Intradermal Injection in Patient and an Individual with No Known Allergies (Control)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Patient</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wheat mm</td>
<td>Flare mm</td>
</tr>
<tr>
<td>0.9% NaCl</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>d-tubo Curare</td>
<td>0.2 mg/ml</td>
<td>&gt;10</td>
<td>30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>500 ng/ml (10^{-6} M)</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>50 ng/ml (10^{-7} M)</td>
<td>—</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>5 ng/ml (10^{-8} M)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.5 ng/ml (10^{-9} M)</td>
<td>—</td>
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was found. Erkkola et al.¹ describe a possible anaphylactoid reaction following the epidural administration of bupivicaine. The clinical events also seem to be compatible with a total spinal: vascular collapse occurred 30 s after drug administration, and the mother was unconscious with a blood pressure of 80/60. The laboratory studies support an immunologic etiology for the events described, but skin testing performed 2 and 3 months later was negative. In any case, it comes as no surprise that anaphylactic responses can occur following epidurally administered drugs. Their very low incidence may be attributable to the rarity of hypersensitivity to the drugs most often given epidurally (local anesthetics and opioids).

Since fentanyl is not associated with an increased blood histamine concentration,² skin testing in conjunction with the appropriate clinical history suggests the diagnosis of anaphylaxis.³,⁴ Fentanyl, in concentrations from 500 ng/ml (10^{-6} M) to 50 µg/ml (10^{-4} M) produces negative intradermal tests in control subjects.³ Levy et al.⁶ showed wheal and flare responses to intradermal fentanyl, as well as sufentanil, but only at a high concentration (5 x 10^{-4} M). Alfentanil at the same concentration showed essentially no wheal and flare response. Meperidine (5 x 10^{-4} M) produced marked wheal and flare reactions, similar to morphine.

My previous exposure to fentanyl supports the diagnosis of hypersensitivity since this probably served as a sensitizing dose. It is possible that I was sensitized to another opioid, and that my response resulted from cross-reactivity. We consider this unlikely, since no adverse responses were noted at the time of fentanyl administration 2 yr before, and there was no exposure to opioids in the interim between the two cesarean sections. Unfortunately, a radioallergosorbent test (RAST) is not yet available for fentanyl. Although classic anaphylaxis includes bronchospasm, this symptom is not always present.⁷ It is interesting to note that bronchospasm was also absent in the other reported subjects with fentanyl hypersensitivity.⁵,⁸

The subsequent skin testing suggests that cross-reactivity does exist between fentanyl, sufentanil, and alfentanil. Naloxone appears not to cross-react. The response to meperidine is more difficult to interpret. Because meperidine causes marked wheal and flare in controls at 5 x 10^{-4} M,⁶ and 10^{-5} M induced a moderate reaction in myself, these probably represent the same nonallergically medicated mechanism. Fortunately, morphine did not elicit any allergic response 3 h and 24 h after the cesarean described, and therefore seems not to cross-react with fentanyl and its derivatives.

In this era of increasing use of epidural fentanyl, especially in obstetrical anesthesia, this Case Report should alert the practitioner to the fact that although fentanyl allergy is extremely rare, and anaphylaxis to an epidurally administered drug has seldom been reported, such events can indeed occur. It appears that in patients with a history of allergy to fentanyl, alfentanil and sufentanil should also be avoided. The safety of meperidine is uncertain. Morphine seems to be a safe alternative, and according to the data presented, the use of naloxone is not contraindicated. We await with (personal) interest further work in this area.

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REFERENCES

Intraoperative ST-Segment Changes Consistent with Myocardial Ischemia in the Neonate: A Report of Three Cases

CHARLOTTE BELL, M.D.,* STEPHEN RIMAR, M.D.,† PAUL BARASH, M.D.,‡

It is commonly believed that monitoring for intraoperative myocardial ischemia is unnecessary in neonates. Whereas electrocardiography (ECG) lead systems for adults are concerned with the detection of ischemia as well as dysrhythmias, neonatal ECG monitoring has focused on dysrhythmia recognition alone. Recent studies, however, suggest that the neonatal heart is more susceptible to ischemia than is the adult heart. The following cases illustrate the value of intraoperative calibrated ECG monitoring for myocardial ischemia in neonates.

CASE REPORTS

Case 1. A 790-g 1-month-old female (26 wk gestation) with a history of respiratory distress syndrome (RDS), intraventricular hemorrhage, and necrotizing enterocolitis presented for ligation of a patent ductus arteriosus (PDA). During awake laryngoscopy 3 mm ST-segment elevations occurred (lead II) without bradycardia and resolved after intubation of the trachea was completed (fig. 1). The anesthetic consisted of fentanyl (10 μg/kg), pancuronium (0.1 mg/kg), and an air/oxygen mixture (FiO₂ = 1.0). During the procedure the lung was compressed without retracting the heart and a 2 mm ST-segment elevation again occurred in lead II with a decrease in heart rate from 180 to 160 beats/min. Both the heart rate and ST-segments returned to baseline when the lung was reexpanded. The patient's recovery was uneventful and postoperative ECG was normal.

Case 2. A 3.5-kg two-day-old full term male with transposition of the great vessels underwent an emergency Senning procedure (resection of venous return via intrathoracic baffle) after an atrial septectomy failed to provide adequate mixing and arterial oxygenation. Induction of general anesthesia with morphine (1 mg/kg) and pancuronium (0.2 mg/kg) was uneventful as was initiation of hypothermic circulatory arrest and cardioplegia. Thirty-five minutes after termination of cardiopulmonary bypass, during chest closure, 3 mm ST-segment elevations occurred in lead II (fig. 2). Increases in heart rate from 150 to 180 beats/min and blood pressure from 100/60 to 110/70 mmHg were noted, and an arterial blood gas demonstrated a pH of 7.24, Pco₂ 42 mmHg, Pao₂ 72 mmHg (FiO₂ = 1.0). Although ST-segments returned to baseline after the administration of dopamine (5 μg·kg⁻¹·min⁻¹), isoproterenol (0.3 μg·kg⁻¹·min⁻¹) and nitroglycerin (3 μg·kg⁻¹·min⁻¹), the patient continued to manifest progressive acidosis and hypotension, which led to electromechanical dissociation and cardiac arrest 12 h postoperatively.

Case 3. A 4-kg three-week-old full-term female presented for elective closure of a large subpulmonic ventricular septal defect (Qp/Qs = 5:1). Inhalation induction with halothane/O₂/Ne₂ and precardiopulmonary bypass maintenance of anesthesia with halothane/morphine/O₂/pancuronium were uneventful. The defect was repaired with a Dacron patch through a right ventricular incision, which was closed with a pericardial patch over the infundibulum. One hour after termination of cardiopulmonary bypass, the patient developed second-degree heart block with 1 mm ST-segment depression (lead II) and periods of ventricular tachycardia (fig. 3). Blood pressure decreased from 80/40 mmHg to 60/20 mmHg, but the ventricular rate remained at 150 beats/min. Arterial blood gas (FiO₂ = 1.0) revealed pH 7.41, Pco₂ 32 mmHg, and Pao₂ 597 mmHg. Blood pressure improved after calcium gluconate (100 mg/kg), dopamine (10 μg·kg⁻¹·min⁻¹), and temporary atrial-ventricular sequential pacing. Upon arrival in the Pediatric Intensive Care Unit, the patient no longer required cardiac pacing and the blood pressure and heart rate were stable at 80/40 mmHg and 150 beats/min, respectively. Postoperative ECG showed a normal sinus rhythm with 1 mm ST-segment depression in leads V₁-V₄, and echocardiogram demonstrated a dilated right ventricle, poor left ventricular function, septal and apical dyskinesis, and mild mitral...