Fentanyl Not an Exception to Anaphylaxis

Mageshwaran Thirunavukkarasu*, Vartika Vinay, Jhansi Eda, Bhavna Gupta

Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Rishikesh, India.

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ABSTRACT

Intraoperative anaphylaxis can lead to significant morbidity and mortality but rarely occurs. Vascular collapse and bronchospasm are the hallmarks of this condition. Numerous agents have been identified as triggers of intraoperative anaphylaxis, the most common being neuromuscular blocking drugs and latex. But opioids rarely cause anaphylaxis. We report an unusual case of intraoperative anaphylaxis with pulmonary edema during a routine plastic surgery procedure was due to iv fentanyl.

Case Report

A 13-yr-old (35kg) female with a history of burns over the face and both hands, was admitted for contracture over the right wrist and posted for contracture release and fat grafting. There was no significant past medical history. Past surgical and anesthetic history showed the patient underwent fasciotomy under sedation. There was no history of drug allergies.

Vital signs were all within normal limits. Her airway, cardiac and pulmonary examinations were normal. Laboratory studies including a complete blood count, electrolytes, kidney function tests were also within normal limits.

After getting written informed consent from his parents, the patient was taken into the operation theatre and all standard ASA monitors were attached. A peripheral line with 20G was secured. After adequate premedication with glycopyrrolate 0.01mg/kg IV and preoxygenation, the patient was induced with fentanyl 2mcg/kg IV, propofol 2mg/kg. Once mask ventilation was found to be easy, vecuronium 0.1mg/kg was given intravenously. Laryngoscopy and tracheal intubation were uneventful. After confirmation of tube placement, the patient has mechanically ventilated with sevoflurane 2% in 50% oxygen and 50% nitrous oxide. Antibiotics were not given.

Approximately 10 minutes after induction but before skin incision, ECG showed brief episodes of SVT (supraventricular tachycardia) 5 to 10 beats per episode. The patient was otherwise stable. Anesthesia was deepened and a total of 15 mg of esmolol IV given in incremental doses. The heart rate rhythm became sinus tachycardia at 144 beats/min over a few minutes. Suddenly patient's blood pressure decreased from 114/75 mm Hg to 65/35 mm Hg. Intravenous fluids were rushed and phenylephrine 50mcg was given which increased BP to 90/65 mm Hg. An ascending slope was noted on the capnogram and peak airway pressure was increased to 35 cm H2O from baseline 12 cm H2O. Chest auscultation revealed bilateral crepitation and the patient's SPO2 decreased from 100% to 90%. FiO2 was increased to 100%. An anaphylactic reaction was suspected and inj. hydrocortisone 150mg, inj. diphenhydramine 50mg, and inj. epinephrine 10mcg was given intravenously. The
patient's blood pressure improved to 125/78 mm Hg. Peak airway pressure was 30 cm H2O, there were no other signs of an anaphylactic reaction. Later frothy secretions were coming out of the endotracheal tube. Frusenide 20mg IV was given. Positive end-expiratory pressure (PEEP) 8 cm H2O was applied to maintain alveolar recruitment. Latex-free foley's catheterization was done. ABG on a Fio2 of 1.0 demonstrated mild metabolic acidosis and mild hypoxemia [PH 7.32, PCO2 41 mm Hg, PO 93 mm Hg with bicarbonate 19.2 meq]. The surgery was canceled and the patient was transferred to ICU. Then central venous cannulation was done for fluid management and an arterial line was inserted for continuous blood pressure monitoring and ABG sampling. Ventilation was continued with PEEP increased to 10 cm H2O. A transthoracic echocardiogram revealed normal chamber size and cardiac function. Serial troponin I values was abnormal, with a peak value of 1.23 ng/ml at eight hours.

Blood and sputum cultures were obtained which yielded no growth. A dermatologist's opinion was done who concurred with the diagnosis of an anaphylactic reaction. A radioallergosorbent test was done with latex and the results were negative. Over 24 hours, the patient's oxygenation improved. Then the patient became conscious, hemodynamically stable. The patient was extubated and kept on facemask oxygen. After 48 hours, an intradermal test was done with midazolam, propofol, vecuronium, fentanyl, atracurium. The results were positive for fentanyl. This was informed to the patient and was asked to avoid fentanyl and other opioids in the future. Later the patient was discharged.

**Discussion**

Anaphylaxis is a fulminant, unexpected IgE mediated allergic reaction that can be triggered by multiple agents. Perioperative anaphylaxis is a life-threatening clinical condition. The agents responsible for anaphylaxis during anesthesia are muscle relaxants, antibiotics, latex, and plasma substitute in the order of frequency [1-2]. In contrast, opioids very rarely cause anaphylaxis [3).

Initial presentations can vary, potentially involving numerous organ systems. The most common system involved is cardiovascular (hypotension, arrhythmia, myocardial depression, cardiovascular collapse), followed by cutaneous (flushing, urticaria) and respiratory (bronchospasm, laryngeal edema) manifestations [1]. During the intraoperative period, there are numerous challenges to diagnose anaphylaxis.

The pathophysiology of anaphylaxis begins with the binding of an allergen to IgE on the surface of mast cells and basophils with crosslinking of receptors and subsequent cell activation. The resultant massive release of mediators such as histamine, leukotrienes, kinins, and eosinophil chemotactic factor leads to bronchoconstriction, vasodilation, and increased capillary permeability. This process can continue, with progressive inflammation leading to a delayed “second wave” of symptoms six to eight hours later [3-4].

Patients receive multiple drugs in close succession, are often unconscious and unable to relate symptoms, and are usually surgically draped, delaying the recognition of cutaneous signs. For patients with clinical signs suggesting anaphylaxis, lab tests including serum histamine test and tryptase test, skin tests such as prick test and intradermal test are useful for a definitive diagnosis although some studies have reported that more than 95% of cases can be diagnosed based on clinical signs alone [5].

A recent survey found that the following agents cause perioperative anaphylaxis in the frequency of decreasing order are rocuronium and succinylcholine accounted for 58.2% followed by latex (16.7%), antibiotics (15.1%), colloids (4.0%), Hypnotics (3.4%) and Opioids (1.3%) [2]. Opioid-induced anaphylaxis is rare. Morphine contains a tertiary amine group which causes an on-immune release of histamine. So, allergic reactions to morphine are much rarer. To date, there have been two reported cases of fentanyl induced anaphylaxis [5-6].

Several features of this case merit discussion. First, pulmonary edema is rarely associated with anaphylaxis but is not without precedent. Its rapid presentation in a relatively young woman with no cardiac disease, a normal echocardiogram, and normal central venous pressures suggests a noncardiac etiology. Since the patient was tracheal intubated and paralyzed, negative-pressure pulmonary edema from airway obstruction seems improbable. Without any increased risk for aspiration or a witnessed event, aspiration pneumonitis also seems unlikely. It is thus reasonable to suspect that anaphylaxis itself was the cause of pulmonary edema, especially as increased capillary permeability is a hallmark of the disorder [7-8]. The elevation in troponin concentrations was concerning. The patient had no history of coronary artery disease and had good functional capacity. A lack of wall motion abnormalities on the postoperative echocardiogram and a subsequent negative stress test suggests that transient ischemia caused subendocardial myocardial injury. Severe vasodilation with insufficient coronary blood flow in the setting of aggressive epinephrine use may have created a significant energy supply-demand imbalance in the myocardium.

The primary treatment of perioperative anaphylaxis begins with avoiding the agent. As soon as anaphylaxis is suspected Fio2 of 1.0 should be given. All anaesthetic agents should be discontinued. Crystalloids like ringer's lactate (2-4 L) or colloids should be given to compensate for hypotension. Injection epinephrine (5-10 μg IV bolus) should be given. In addition to the above-mentioned
secondary treatment with bronchodilators, bicarbonate, vasopressin can be tried [9].

**Conclusion**

Anaphylaxis can be caused by any anaesthetic agent opioids like fentanyl are not an exception. Adequate preparation to handle anaphylaxis at right time can save the life of both anaesthesiologist and the patient.

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