Anaphylactic reaction during anaesthesia associated with positive intradermal skin test to fentanyl

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A 29 year-old female patient suffered vascular collapse which became apparent immediately after general anaesthesia. Resuscitation was prolonged and difficult, and complicated by the need for reoperation. Based on the time history, fentanyl was suspected as the causative agent. Fentanyl allergy was confirmed by skin testing one month later. The case is discussed, and the possible reasons for the delay in appearance of symptoms and signs are considered.

Anaphylaxis is a rare but life threatening systemic allergic reaction which may present as "primary vascular collapse without antecedent respiratory difficulty." This quotation, from Austen's 1974 review of anaphylaxis,[1] describes exactly the presentation of the following case.

Anaphylactic reactions to narcotics must be exceedingly rare and have not previously been definitely associated with fentanyl alone. We wish to report a case of vascular collapse, generalized erythema and urticaria following the administration of fentanyl in a patient in whom fentanyl allergy was later confirmed by intradermal testing.

Key words
ALLERGY: fentanyl anaphylaxis; ANALGESICS: fentanyl; COMPLICATIONS: hypotension.

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Case report

A 29-year-old female nurse was admitted for lumbar laminectomy. She had a two year history of right leg pain unrelieved by laminectomy 11 months prior to the present admission. She also had the mitral valve prolapse syndrome with paroxysmal atrial tachycardia, controlled with nadolol 40 mg qd. A prolactin secreting pituitary adenoma had been removed by subtotal transphenoidal hypophysectomy four years prior to admission. Reoperation was required by persistent cerebrospinal fluid leak. All operations were performed with general anaesthesia using thiopentone, pancuronium, succinylcholine, and either halothane or enflurane. There was no record of prior fentanyl administration. Endocrine evaluation of the pituitary axis was normal seven months prior to the present admission; in particular, ACTH reserve was normal. An allergic reaction manifested by angioneurotic oedema and urticaria occurred after oral zomepirac. There was no other history of allergy.

On preoperative physical examination, there was a grade II/IV systolic murmur over the left sternal margin; weight was 55.2 kg; blood pressure 110/70 mmHg (15/9 kPa) and pulse rate 76 beats/min and regular. Admitting general laboratory studies, electrocardiogram (ECG) and chest roentgenogram were normal except for non-specific ST-T wave abnormalities on the ECG. The haematocrit was 38 per cent. The last dose of nadolol was given 24 hours preoperatively.

Anaesthesia was induced with diazepam 5 mg and thiopentone 4 $mg \cdot kg^{-1}$. Tracheal intubation was facilitated with succinylcholine 1.5 $mg \cdot kg^{-1}$. Anaesthesia was maintained with N_2O 67 per cent

and enflurane one to two per cent as needed to maintain systolic blood pressure between 90 and 110 mmHg (12 to 15 kPa). Nafcillin 2.0 g was given prior to induction and pancuronium 0.05 $mg \cdot kg^{-1}$ was given before the skin incision. The solution used for surgical site preparation contained fluorescent pink dye. The procedure was performed with the patient in the prone position. Surgery was uneventful for two and one-half hours. During closure of the incision, fentanyl 0.05 mg was given, followed in approximately ten minutes by neostigmine 2.0 mg and atropine 0.8 mg. Over the next hour, cessation of enflurane administration and the rapid infusion of an additional liter of Ringer's lactate were required to maintain systolic blood pressure at or above 80 mmHg (11 kPa). Heart rate remained at 76. At the time, this was felt to be unusual but was attributed to possible unrecognized blood loss. Following wound closure and dressing, the patient had resumed spontaneous ventilation and was returned to the supine position. She immediately opened her eyes in response to name and the endotracheal tube was removed. She was transferred to the recovery room, arriving 70 minutes after fentanyl administration. Fluid volumes for the procedure were: blood loss 200 ml, no replacement, urine output 380 ml, crystalloid administered 3000 ml.

Upon arrival in the recovery room, the patient was moving and attempting to talk; her blood pressure was unobtainable by auscultation. She had palpable central pulses. With the aid of doppler detection, her systolic blood pressure was determined to be 40 mmHg (5 kPa). Her heart rate was 80 with a normal complex on the electrocardiograph. She had generalized erythema and rapidly developed cyanosis of the nail beds. She was given oxygen by mask, placed in the Trendelenberg position, given ephedrine 10 mg IV and a rapid infusion of 500 ml lactated Ringer's solution. With these measures, her blood pressure rose to 70 mmHg (9 kPa) systolic. Arterial blood gases (F_IO_2 0.40) were: pH 7.29, PCO_2 33 mmHg (5 kPa), PO_2 183 mmHg (24 kPa). Serum sodium was 142 $mEq \cdot L^{-1}$, potassium 3.6 $mEq \cdot L^{-1}$ and haematocrit was 34 per cent.

During the next hour the erythema became an urticarial rash. Hydrocortisone 100 mg was given immediately, following by dexamethasone 20 mg. Six hundred and fifty μg of epinephrine were given slowly IV, followed by a continuous infusion of epinephrine. An additional 2500 ml of crystalloid and one unit of packed red cells were given during this period to maintain blood pressure. By this time she was beginning to develop generalized oedema. Chest and abdominal roentgenograms were normal. There were no obvious murmurs suggestive of mitral regurgitation, no rales, no wheezing and no gallops. During an attempt at insertion of a flow-directed pulmonary artery catheter into the right internal jugular vein, one of the arteries in the neck was catheterized. Operative removal of the catheter was felt necessary because of the patient's unstable haemodynamic status. The provisional diagnosis was anaphylactic reaction to an unknown antigen and laceration of a major artery.

For the second operation, anaesthesia was induced with etomidate 30 mg in divided doses. Intubation was facilitated by pancuronium 0.1 $mg \cdot kg^{-1}$. Anaesthesia was maintained with isoflurane 0–1.0 per cent as tolerated and incremental doses of ketamine (total 50 mg) and fentanyl (total 0.2 mg). The catheter was removed from the right subclavian artery and the arterial laceration repaired. Throughout the procedure, the patient continued to require circulatory support with an epinephrine infusion and the administration of massive fluid volumes to maintain blood pressure. Pulmonary artery occlusion pressures varied between 2 and 12 mmHg (0.3 to 1.4 kPa). Except for a slight increase in ventilation pressure during the course of the operation, there was no evidence of pulmonary dysfunction.

Inotropic and chronotropic support were required for sixteen hours. An additional 12 liters of fluids were required to maintain systemic arterial pressure and pulmonary artery occlusion pressure during the period. Diuresis began at the end of this period and recovery was rapid thereafter. The hematocrit was 32 per cent during the second postoperative day, increasing to 34 per cent by the time of discharge on the twelfth postoperative day. There were no immediate sequelae of the episode but two months later the patient complained of loss of strength and pain in the right arm.

Intradermal testing

Four weeks after the events described, we performed intradermal testing of our patient for all of the drugs given during the last two and one half hours of surgery (neostigmine, atropine and

fentanyl). She was still taking nadolol 40 mg qd. We used the test protocol of the Allergy Clinic of the Oregon Health Sciences University. The procedure was similar to the "prick test" described by Nelson[2] except involving smaller quantities of material (estimated 0.25 μl). Histamine (0.1 $mg \cdot ml^{-1}$) was used as a positive control and normal saline was used as a negative control. All histamine tests produced at least a 4 mm wheal and flare response (the usual positive for this test); the saline tests produced no wheal and flare. A minimum of ten minutes was allowed between successive tests. Tests were read at fifteen minutes.

Our patient was tested with progressively increasing concentrations of neostigmine methyl sulfate, atropine sulfate and fentanyl citrate from the same drug lots as had been used during the operation. The first tests were with 10^5 dilutions of the stock solutions, then 10^4 dilutions, etc., finishing with the full strength stock solutions. The stock solution concentrations were 1.0 $mg \cdot ml^{-1}$, 0.8 $mg \cdot ml^{-1}$ and 0.05 $mg \cdot ml^{-1}$ for neostigmine, atropine and fentanyl, respectively.

We also tested five normal volunteers (two were atopic, three were not; one was taking propranolol) with all of the fentanyl dilutions.

Our patient did not respond to any dilution of neostigmine or atropine. She had a 5 mm wheal and flare response to the lowest concentration of fentanyl solution (0.5 $ng \cdot ml^{-1}$). After waiting 20 minutes, she was tested with 10^4 dilutions of fentanyl (5.0 $ng \cdot ml^{-1}$) and had a 6 mm wheal and flare response (this is a strong positive for this test). Testing with fentanyl was terminated at this point.

None of the volunteers responded to any concentration of fentanyl, although all had a wheal and flare reaction to histamine. Fisher* has also tested 30 normal patients to fentanyl citrate (500 $ng \cdot ml^{-1}$) and found no positive responses.

Discussion

Anaphylactic reactions to narcotics must be extremely rare. Fisher has reviewed the diagnosis,[3] epidemiology and clinical presentation[4] of anaphylactic reactions in anaesthesia and noted no prior cases of anaphylaxis to fentanyl. The only previous case report of possible fentanyl anaphylaxis occurred in a patient who received a number of drugs intraoperatively and subsequently had positive intradermal tests to fentanyl and alloferin, both of which had been used intraoperatively.[5]

Our patient presented with primary vascular collapse with urticaria without pulmonary involvement. Although profound hypotension did not occur until an hour after the first administration of fentanyl, during that period fluid requirements increased considerably and anaesthesia was not well tolerated, suggesting the possibility that the initial hypotension was promptly and successfully treated without recognizing it as an early sign of anaphylaxis. Only when the insult to capillary permeability had manifested itself by massive fluid shifts was the possibility of drug reaction entertained. Early cutaneous manifestations would not have been visible because of the presence of surgical drapes and the pink dye from the scrub solution. Delayed anaphylaxis can also occur.[6] It is also possible that general anaesthesia modified the initial presentation of anaphylaxis.

It is not clear what influence, if any, the additional doses of fentanyl given during the second operation may have had on the course of the reaction. However, once antigenic challenge causes mast cells to degranulate, further release must await synthesis of mediators and immediate rechallenge with antigen produces no additonal mediator release.

This patient had one risk factor for anaphylaxis, namely the previous allergic reaction to zomepirac. In addition, she was taking a beta adrenergic blocking drug which might enhance the release of mediators of anaphylaxis[7] and which might also decrease the effectiveness of therapeutic epinephrine (her pulse rate increased in response to epinephrine, however).

The fentanyl allergy was confirmed using intradermal testing one month after the reaction occurred. According to Fisher[3] and Nelson,[2] more sophisticated tests add little information to skin testing when dealing with drugs which do not release histamine. Fentanyl administration is not associated with increases in blood histamine[8] and none of our test subjects had positive intradermal tests to fentanyl in any concentration tested, in agreement with Fisher's previously cited results. Therefore, the positive wheal and flare reaction

*M.M. Fisher, personal communication, 1984. Address: Royal North Shore Hospital, St. Leonards 2065, New South Wales, Australia.

seen in our patient indicates the presence in her skin mast cells of specific IgE antibodies to fentanyl and this confirms fentanyl allergy.

There is no documentation of our patient having received fentanyl previously. It is possible that an unrecorded dose of fentanyl was given during one of her previous anaesthetics, or that she had been exposed to the drug during her work as a physician's office nurse, or that she was sensitized to another phenylpiperidine such as meperidine or diphenoxylate and cross-reacted to fentanyl. Anaphylaxis to meperidine has been reported.[9] According to the records, she had received several doses of meperidine for analgesia during her previous hospitalizations. Intradermal testing for allergy to meperidine would yield little information since meperidine administration is associated with direct pharmacologic histamine release.[10] A radioallergosorbent test is not available for fentanyl.

This is a definite case of anaphylactic reaction and the positive skin test to fentanyl makes this drug a likely putative agent. A classic anaphylactic reaction with bronchospasm, hypotension and urticaria most often occurs closely after the administration of the antigenic substances. However, the occurrence, severity and time of appearance of the signs of anaphylaxis are all highly variable. In addition, during anaesthesia many drugs are given and the anaesthetic itself may modify the signs. This reaction manifested itself following an anaesthetic by primary vascular collapse without respiratory difficulty, although in retrospect vasodilation and hypotension probably occurred immediately. The reaction was not recognized until the delayed consequences of the insult to vascular permeability became evident. This case report indicates that anaphylaxis must be considered as part of the differential diagnosis of any case of profound hypotension perioperatively, and that fentanyl allergy is a possible cause.

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Résumé

Un patient a démontré un choc cardiovasculaire ayant apparu immédiatement après l'anesthésie générale. La réanimation était prolongée et difficile et compliquée par une réopération. En se basant sur l'histoire chronologique, le fentanyl a été suspecté comme étant l'agent causal. L'allergie au fentanyl a été confirmée par des tests cutanés un mois plus tard. Le cas est discuté et les raisons possibles pour le délai dans l'apparition des symptômes et des signes est discuté.