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Case report

Intraoperative recurrence of probable allergic reaction to remifentanyl. Case report[☆]



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ABSTRACT

Introduction: Although rare, intraoperative anaphylaxis may be life-threatening. Opioids, including remifentanyl, have the lowest rates of association with allergic reactions during anaesthesia. Recurrence of anaphylactic reaction after continuation of a remifentanyl infusion creates the suspicion of a causal relationship between this agent and the reaction. **Case description:** Case presentation of anaphylactic reaction during balanced anaesthesia in a 19 year-old female patient. At the start of the surgical procedure, the patient developed refractory hypotension and generalized erythema, which responded to vasopressors, antihistamines and the discontinuation of the anaesthetic agents. The remifentanyl infusion was reinitiated later in response to the need of increasing the depth of the anaesthesia, and the anaphylactic reaction recurred.

Conclusion: Any medication or potential allergen to which a patient is exposed during the perioperative period may cause anaphylaxis; the usual culprits are neuromuscular blocking agents (NMBA). In 80% of cases of hypersensitivity to medications, the origin is not immunological; the only way to confirm anaphylaxis is by means of biological and skin testing performed in a unit specializing in allergy and anaesthesia. In this case, confirmation was not possible because, in Colombia, the specific technological and biological resources are lacking.

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Reincidencia intraoperatoria de probable reacción alérgica al remifentanilo. Informe de caso

RESUMEN

Introducción: La aparición de anafilaxia intraoperatoria es rara pero amenaza la vida de los pacientes. Los opioides son los agentes que menos producen reacciones alérgicas en

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anestesia, entre ellos el remifentanilo. La reincidencia de la reacción anafiláctica al continuar la infusión de remifentanilo hace particularmente sospechoso este agente como causante de la reacción.

Descripción del caso: Se presenta el caso de una reacción anafiláctica durante anestesia balanceada en una paciente de 19 años. Al inicio del acto quirúrgico la paciente presenta hipotensión refractaria y eritema generalizado, que responde al manejo con vasopresores, antihistamínicos y suspensión de los anestésicos. Posteriormente se requiere aumentar la profundidad de la anestesia por lo cual se reinicia infusión de remifentanilo y la reacción anafiláctica reaparece.

Conclusión: Cualquier medicamento o posible alérgeno al cual sea expuesto un paciente en el perioperatorio puede ocasionar anafilaxia; los medicamentos más involucrados son los bloqueantes neuromusculares (BNM). El 80% de los eventos de hipersensibilidad a medicamentos no es de origen inmunológico; la única manera de confirmar una anafilaxia es mediante pruebas biológicas y pruebas cutáneas realizadas en una unidad especializada en alergia y anestesia. Este caso no pudo confirmarse debido a que en Colombia no existe este recurso técnico y biológico específico.

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Introduction

Anaphylaxis during anaesthesia is a rare event but may be life-threatening for the patient. It is the most serious form of an adverse reaction to medications, blood or latex.¹ The number of medications and potential allergens to which patients may be exposed during the perioperative period ranges between 7 and 9.²⁻⁴ The incidence of anaphylaxis during anaesthesia varies depending on the different reports: in Denmark, it ranges between 1:10 000 and 1:20 000,⁴ in the United States between 1:13 000 and 1:20 000,⁵ and in Poland between 1:6000 and 1:20 000.⁶ The true incidence and associated morbidity and mortality are poorly defined⁷ because anaesthetists can very rarely identify the cause of an allergic reaction during anaesthesia.

The lack of reports and information regarding anaphylaxis during anaesthesia is due mainly to the fact that symptoms may be similar to anaesthetic-related side effects and that reactions to various antigens in different clinical situations are different and depend on prior exposure to the antigen; histamine release by barbiturates and opioids is frequent and may trigger non-immune reactions similar to anaphylaxis.

Anaphylaxis is an immediate hypersensitivity IgE-mediated reaction or a type I allergic reaction in individuals previously exposed to a medication. In patients who develop allergic reactions to medications when first exposed to anaesthesia, these are usually non-allergic hypersensitivity reactions.⁶

The European Academy of Allergy and Clinical Immunology (EAACI) defines anaphylaxis as any severe systemic life-threatening reaction caused by allergic and non-allergic hypersensitivity. The term "allergic" must be used whenever reactions are mediated by IgE or immune complexes, while "non-allergic" applies in cases of non-immunologically-mediated reactions.⁶

In anaesthesia, the main agents that may produce hypersensitivity reactions include: neuromuscular blocking agents (NMBA) (62%), latex (16.5%), I.V. anaesthetics (7.4%), antibiotics (4.7%), colloids (3.6%) and opioids 1.9%.⁸ Allergic reactions to morphine, codeine, fentanyl, remifentanyl and opioid derivatives are rare because they release histamine directly without giving rise to an allergic reaction as such.⁹

Only 6–10% of adverse reactions to medications are immunologically-mediated, and 80% of all drug-related adverse reactions (RAD) are secondary effects associated with toxicity, overdosing and side effects.¹ In Colombia there is no referral institution for patients in whom anaphylactic reactions during anaesthesia are suspected. Consequently, there is a need to use causality algorithms such as the Naranjo (WHO)¹⁰ or the FDA algorithms.

Case report

A 19 year-old female patient coming from Tunja, admitted to the hospital for planned surgical ileostomy closure and abdominal mesh placement.

History: Hip arthrotomy in childhood, poliomyelitis sequelae. Laparotomy two years before because of peritonitis secondary to perforated appendicitis, with performance of hemicolectomy and ileostomy. The patient had received general anaesthesia on two occasions in the past, with no complications. Allergic to dipyrone.

Physical examination: The patient is alert, oriented, in good general condition; blood pressure (BP) 110/60 mm Hg, heart rate (HR) 68 beats/min, respiratory rate 17/min, weight 71 kg; normal cardiopulmonary function; Mallampati I; colostomy bag and large abdominal wall eventration. MMII muscle group atrophy secondary to infantile poliomyelitis.

Laboratory tests: Haemoglobin 15.8 g/dL, haematocrit 45%, with normal differential formula; no eosinophilia and normal INR.

Monitoring: 2D visoScope, pulse oximetry, non-invasive blood pressure and capnography; peripheral venous access with 18G catheter in right upper limb.

Induction: Midazolam 1mg, fentanyl 150 µg, propofol 120 mg, vecuronium 4mg. Easy, uncomplicated endotracheal intubation with No. 7 tube, volume-controlled mechanical ventilation. An infusion of remifentanyl 0.2 µg/kg/min and 1% sevoflurane was started at 7:50 a.m. Induction was followed by dexamethasone 8mg, ranitidine 50mg and metoclopramide 10mg. Initial vital signs were blood pressure 130/80 mm Hg, heart rate 85 beats/min and saturation 98%. Five minutes into the anaesthesia (7:55 a.m.) blood pressure dropped to 90/60 mm Hg and heart rate to 60 beats/min. Ringer's lactate infusion was continued at 100 ml/h.

The surgical procedure started at 8:00 a.m., and BP remained at a low level. Fifteen minutes later (8:20 a.m.), the patient was still hypotensive at a BP level of 70/50. A bolus of 50 ml of crystalloids and etilefrine 3 mg was administered. Despite repeated doses of etilefrine up to 15 mg, there was no response and another peripheral venous access was established. At 8:50 a.m., external jugular vein access was established with a 16G needle. At this point, generalized erythema was observed in the upper limbs, chest, dorsum and neck. Suspecting an anaphylactic reaction, remifentanyl and sevoflurane were discontinued, followed by hydrocortisone 100 mg, and dopamine was started at 5 µg/kg/min. At 9:20 a.m., the dopamine drip was exchanged for noradrenaline 0.1 µg/kg/min. Blood pressure increased and the generalized erythema had disappeared by 10 a.m.

At 10:15 a.m. the patient showed signs of emergence from anaesthesia, so she was given ketamine 50 mg and tramadol 100 mg. Upon reinitiation of the remifentanyl drip 0.16 µg/kg/min (10:25 a.m.), the patient again developed generalized erythema and hypotension at 63/32 and HR at 45/min. Remifentanyl was discontinued again, noradrenaline was increased to 0.2 µg/kg/min and parenteral fluids were also increased to 500 ml/h. When BP was recovered, clemastine 2 mg IV and 3% sevoflurane were administered. The patient did not present desaturation or bronchospasm.

At the end of the procedure (11:45 a.m.), the patient was extubated and transferred to the post-anaesthetic recovery unit on the norepinephrine drip. She remained 3 h in recovery and after that time she was discharged to the floor with no inotropic support. She was discharged after 12 days in the hospital, during which time she did not present other signs of allergy.

A score of 6 was obtained with the application of the Naranjo (WHO)¹⁰ algorithm to assess causality of the allergic reaction to remifentanyl. This category was interpreted as "probable".

Discussion

At the present time, remifentanyl is the most widely used opioid as part of general balanced anaesthesia. Dong et al.¹¹ from the Perianaesthetic Allergic Reactions Study Group in France (GERAP), in their ninth research conducted between 2005 and

2007, reported just one case of allergic reaction to remifentanyl among 786 cases of anaphylaxis.

In the case reported here, there are two factors in the Naranjo algorithm that point to a probable adverse reaction to remifentanyl: the onset of symptoms with the administration of the drug, and their reappearance immediately after the infusion was reinitiated.

Since 1980, 4800 cases of perioperative anaphylaxis documented by biological material and skin testing have been reported in France and Denmark.^{12,13}

The confirmatory sequence for an anaphylactic reaction during anaesthesia is as follows: clinical history, chronology of the events, results of tests in biologic material and, finally, skin tests. Biological tests consist of triptase and histamine measurements in blood. Triptase blood levels greater than 10 µg/L are suggestive of allergic reactions, whereas high histamine plasma levels and methylhistamine urine levels confirm excess release of this substance in vivo. Dewachter et al.¹⁴ refer to three forms of diagnostic evidence: presumed, based on clinical findings; histamine and triptase plasma levels which must be measured before 48 h and which, for many are not necessarily confirmatory of the diagnosis; and, finally, skin tests performed 4–6 weeks after the reaction. The remifentanyl concentration, normally non-reactive in skin tests, is 0.05 mg/ml.¹⁵ Phenylpiperidines are the opioids most frequently implicated in anaphylactic reactions.¹⁶ In the case presented here, only the first step in the diagnosis was completed.

Krøggard et al.⁴ from the Danish Allergy and Anaesthesia Centre conducted a retrospective study between 1999 and 2003 with 108 patients clinically diagnosed with a perioperative anaphylactic reaction. The suspected causal agent was identified in 67 of them, while in 44 no indication was found about the cause. The most serious cases classified as grade III in the Ring and Messmer¹⁷ classification were those in whom there was a suspected agent. In 49 of the 67 cases in which there was a suspected agent, tests were not confirmatory, and only in 5 of them (7.5%) was the diagnosis confirmed. This study dismisses the value of biological and skin tests for confirming the causal agent of anaphylaxis.

In a 10-year research in Belgium, Laysen et al.,¹⁸ reported 344 patients who developed anaphylaxis during anaesthesia and were referred to a specialized allergy and anaesthesia centre. Of these, 72% were found to be IgE mediated, and no opioid-related cases were identified.

For Baldo and Pham,¹⁹ more than reactions to histamine release, opioid-related adverse reactions are anaphylactoid reactions predominantly with skin manifestations, and hypotension, when it occurs, is probably due to anaphylactic reactions. The clinical picture of our patient is consistent with this latter description.

Although many authors tend to believe that opioid-related reactions are due to direct mast cell degranulation with absence of specific IgE antibodies, some studies have shown skin release of histamine in mast cells following mast cell stimulation with morphine or other tissues such as lung, heart, and gastrointestinal tract, as well as in basophils. Synthetic opioids such as fentanyl, alfentanil and remifentanyl are rarely associated with anaphylaxis, they do not release

histamine directly, and IgE is believed to be the mechanism by which the reaction is produced, mechanism that can be investigated using skin tests.²⁰

Failure to confirm the suspected agent is a common occurrence in perioperative allergic reactions. In the case of our patient, the history of allergy to dipyrone reinforces the probability of anaphylaxis, because the administration of diclofenac after the induction may account for a cross-reaction between NSAIDs.²¹

Likewise, neuromuscular blocking agents with quaternary ammonium in their structure have been associated with the occurrence of allergy and cross hypersensitivity and they are the most frequent cause of anaphylaxis.¹⁴ Vecuronium, also administered in this case, is responsible for 28.8% of allergic reactions to NMBAs.

Every patient with suspected serious allergic reactions during anaesthesia must be studied to determine the possibility of IgE-dependent reactions, and the anaesthetist is responsible for ensuring that the patient is referred to an allergy and anaesthesia centre.²²

The criteria for referring a patient to a specialized centre are: unexplained cardiac arrest during anaesthesia, unexplained and unexpected hypotension (mean BP fall greater than 30 mm Hg requiring acute treatment), severe unexplained bronchospasm with desaturation, generalized skin rash or significant urticaria, and angioedema.¹⁴

Although there is no general agreement regarding the definitive value of skin and biological tests for the diagnosis of anaphylaxis, they should be requested whenever possible considering past rulings of malpractice liability in cases of adverse events that were not adequately investigated.²³

Conclusions

Given the clinical presentation of the event, an anaphylactic reaction to remifentanyl is considered probable. However, confirmation was not possible because of the strange occurrence and the lack of biological and skin tests. There is no consensus in the literature regarding the true value of biological and skin tests, and there is a need to create a specialized unit for allergy and anaesthesia in our country in order to collect epidemiological and perioperative anaphylaxis confirmation data, even more so given the fact that jurisprudence endorses such procedures.

Ethical approval

Publication of this article was endorsed by the Ethics Committee of the Hospital.

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Conflicts of interest

None.

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