

Case report

Intraoperative anaphylactic shock to nefopam

*Choc anaphylactique peropératoire au néfopam*R. Boubakr^{a,b}, O. Nahas^{a,*}, H. Belbaali^a, S. Baali^a, P. Demoly^{a,c}, A.M. Chiriac^{a,c}^a Department of pulmonology, division of allergy, hôpital Arnaud de Villeneuve, university hospital of Montpellier, Montpellier, France^b Service de médecine polyvalente A, centre hospitalier de Chaumont, Chaumont, France^c Équipe-EPAR-IPLESP, UMRS 1136, UPMC université Paris 06, Sorbonne universités, Paris, France

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Abstract

Diagnosis of IgE dependant intraoperative anaphylaxis is supported by increased serum tryptase levels at the time of reaction. Nefopam is a centrally acting non-opioid analgesic drug widely used for the relief of moderate to severe pain as an alternative to opioid analgesic drugs. We report a case of an intraoperative IgE-dependent anaphylactic shock to nefopam, diagnosed by skin prick testing.

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Keywords: Nefopam; Shock; Intraoperative anaphylaxis; General anesthesia; Skin tests

Résumé

Les réactions anaphylactiques peropératoires entraînent principalement une augmentation de la tryptasémie sérique au moment de la réaction. Le néfopam est un analgésique non-opioïde à action centrale, largement utilisé pour le soulagement d'une douleur modérée à sévère comme alternative aux médicaments analgésiques opioïdes. Nous rapportons un cas de choc anaphylactique IgE dépendant peropératoire au néfopam, diagnostiqué par des tests cutanés.

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Mots clés : Néfopam ; Choc ; Anaphylaxie peropératoire ; Anesthésie générale ; Tests cutanés

1. Introduction

Anaphylactic reactions are immune-mediated allergic reactions. Diagnosis of IgE-dependent anaphylaxis is supported by increased serum tryptase levels at the time of reaction [1]. The three mainly causes of intraoperative anaphylactic shock are muscle relaxants, antibiotics and latex allergy [1]. We report herein a case of an intraoperative IgE-dependent anaphylactic shock to nefopam.

2. Report of case

Nefopam is a centrally acting non-opioid analgesic drug of the benzoxazocine chemical class marketed in France since 1981 [2]. It is widely used for the relief of moderate to severe pain as an alternative to opioid analgesic drugs [3].

We report the case of a 56-year-old female patient, hospitalized in April 2012 for left lumpectomy under general anesthesia.

She received fifteen minutes before induction cefazoline as antibiotic prophylaxis. Anesthesia was induced by propofol and sufentanil and maintained by sevoflurane. Analgesia consisted in nefopam and ketoprofene.

Cardiovascular state was stable under general anesthesia and during the 15 first minutes of injection of dexamethasone, pantoprazole and nefopam given as a continuous intravascular

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Table 1

Skin testing (prick and intradermal tests) and drugs challenge test dosage, following previous recommendations [4–6].

Drug	SPT maximal concentration	IDT maximal concentration	Challenge test (total dosage) (mg)
Nefopam	10 mg/mL	ND	ND
Sufentanyl	5 µg/mL	0,5 µg/mL	ND
Propofol	10 mg/mL	1 mg/mL	ND
Dexamethasone	4 mg/mL	0,4 mg/mL	8
Ketoprofen	100 mg/mL	0,1 mg/mL	136
Cefazolin	2 mg/mL	2 mg/mL	2000

IDT: intradermal testing; SPT: skin prick test.

infusion during 30 minutes. However, 15 minutes later, anesthesiologist administered ketoprofen and a cardiovascular shock occurred within minutes. Shock was corrected with vascular loading and adrenaline.

The shock was successfully treated by intravenous epinephrine and vascular filling with IV hydroxyethyl starch. Upon recovery, the surgical intervention was continued.

Two months later, the patient was addressed to allergy consultation in order to find the agent responsible of the reaction. Prick and intradermal tests (IDT) were performed as recommended [4,5] (Table 1). They were all negative for the tested agents except with nefopam. A pure solution of nefopam, at a concentration of 10 mg/mL, was used for skin prick test inducing strongly positive response (12 mm) that remained till a 10^{-4} dilution (6 mm). Given the lack of knowledge about nefopam skin testing, prick tests to nefopam were done in 10 asymptomatic controls. They were negative in all cases at the 10 mg/mL concentration.

Skin prick test to latex was negative.

Biological measurement performed after recovery, showed high levels of serum tryptase and histamine: tryptase 49 µg/L (normal < 10 µg/L), histamine > 2.0 nmol/L (normal < 10.8 nmol/L). Specific IgE to latex, using ImmunoCAP phadia dosage k82 (ThermoFisher Scientific®), was 0.14 kUA/L.

Negative skin tests were followed by intravenous drug challenge tests for cefazolin, dexamethasone, pantoprazole, and oral challenge test for ketoprofen (Table 1). Step increase followed our previously described protocols [6], up to full therapeutic dose administered during the general anesthesia. All these tested drugs turned out negative.

Paracetamol was not tested since it was reintroduced after surgery without allergic symptoms.

Povidone-iodine (betadine) was the topical antiseptic solution used during surgery, and was not tested since it was reintroduced after surgery with no allergic reactions.

Due to the association of clinical signs, elevated concentrations of histamine and tryptase and the positivity of skin prick

tests to nefopam and its strong pharmacological imputability criteria (imputability score: 14 according to Begaud et al. classification [7]), we concluded to the diagnosis of immediate allergic hypersensitivity reaction to nefopam.

3. Discussion

An analysis of the French Pharmacovigilance database about adverse drug reactions (ADR) to nefopam, was conducted between 1995 and 2004 [2]. A total of 324 cases were recognized. The most frequent ADR registered were antimuscarinic effects. In this database, unexpected cases of ADR to nefopam included 6 cases of anaphylactic reactions. Four of these six cases were anaphylactic shocks and two were angioedemas. All anaphylactic reactions occurred shortly after nefopam administration during the postoperative period. In this French Pharmacovigilance database analysis, nefopam incrimination in anaphylactic reactions was based solely on pharmacological imputability score without performing any allergy testing, so the role of co-administered drugs in all cases could not be ruled out [7].

To our knowledge, there are no documented IgE-dependent cases to nefopam reported in the literature. Due to the lack of standardized skin testing to nefopam, the concentration of 10 mg/mL has been tested with prick tests in ten asymptomatic non-exposed controls and was negative in all ten cases.

Disclosure of interest

The authors declare that they have no competing interest.

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