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Intraoperative anaphylaxis: a case report of allergy to ranitidine

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Summary
We report the case of a 18-year old male who developed intraoperative anaphylaxis. The presence of specific IgE to ranitidine was documented. This case confirms the possibility of anaphylaxis at first exposure.

The incidence of intraoperative anaphylaxis ranges from 1 in 10000 to 1 in 20000 (1) and is fatal in 0.65-2% of cases (2). The most common causes of anaphylaxis during anaesthesia are the use of neuromuscular blocking agents (58.08%), latex (19.65%) and antibiotics (12.85%), although any drug can be implicated (3).

We report a 18-year-old boy who underwent surgery for mandibular reconstruction following a post-traumatic fracture. He had a past history of parietaria and grass pollen-induced seasonal allergic rhinitis, but was otherwise healthy and not on medication.

Forty-five minutes after induction of anaesthesia (Propofol, Remifentanil, Cisatracurium, Sevofluorane), and during the slow intravenous infusion of 50 mg of ranitidine, 4 mg of ondansetron, 4 mg of dexamethasone and 80 mg of tramadol, the patient developed spontaneous tachycardia (heart rate increased from 60 to 122 pulse/min) and hypotension (from 110/60 to 68/35 mmHg). There was also an increase in peak pressure from 22 to 36 cmH_2O with simultaneous diminished vesicular breathing, especially in the left lung. A chest X-ray ruled out left-sided iatrogenic pneumothorax, and bronchospasm due to sevoflurane was hypothesised. The gas was discontinued and replaced by propofol, moreover an intravenous urgent therapy of hydrocortisone and norepinephrine was administered. Serial blood samples for serum tryptase determination were taken. A gradual improvement in the patient's ventilatory and hemodynamic status resulted and the norepinephrine was stopped once he was fully stabilized, enabling surgery to proceed. Intraoperative anaphylaxis was suggested by case history and by increased levels of serum tryptase (19.1 and 21.5 μ/l 1 hour and 3 hours respectively following the onset of the reaction) compared to the normal value of this marker (<11.5 μ/l – Phadia), as well as the patient's basal levels which measured 8.7 and 5.5 μ/l five days and one month following the event.

One month later the patient was given an allergological work up versus a wide panel of anaesthetic drugs (Tab. 1). Skin prick tests were also performed with histamine and saline solution used as positive and negative controls respectively.

Table 1 - The panel of allergens and their dilutions used for the allergological work up

Drug	Prick	Result	ID*	Result
Atracurium Tracrium® 10 mg/ml	1/10	Neg	1/1000	Neg
Cisatracurium Nimbex® 2 mg/ml	non-diluted	Neg	1/100	Neg
Propofol Diprivan®10 mg/ml	non-diluted	Neg	1/10	Neg
Thiopental Pentothal®25 mg/ml	non-diluted	Neg	1/10	Neg
Vecuronium Norcuron® 4 mg/ml	non-diluted	Neg	1/10	Neg
Rocuronium Esmeron®10 mg/ml	non-diluted	Neg	1/100	Neg
Atropine Atropina®0.5 mg/ml	1/100	Neg	1/100	Neg
Midazolam 5 mg/ml	non-diluted	Neg	1/10	Neg
Remifentanil Ultiva®1 mg/ml	non-diluted	Neg	1/10	Neg
Latex (ALK)	non-diluted	Neg		
Ranitidine Ranidil®10 mg/ml	non-diluted	32 mm^2		
Histamine		31 mm^2		
Saline solution		Neg		

* intradermal test

Table 2 - Levels of the serum IgE specific to ranitidin and control measured using the epoxy-activated sepharose radioimmunoassay

Date of collection	Total IgE	IgE specific to Ranitidine (% Uptake)	Control serum (sepharose aspecific binding %)
10/09/10	167 KU/L	6	1.08
29/7/11	158 KU/L	5.35	1.07

Specific IgE for gelatin were absent (Immuno-CAP, Phadia).

The skin prick test with ranitidine was negative in eight healthy controls. Serum-specific IgE against ranitidine were assayed by radioimmunoassay using epoxy-activated sepharose 6B as a solid phase following Baldo's method (4) (Tab. 2). A threefold increase over the cutoff level was documented.

Ten months later the patient was reassessed for allergy to ranitidine. The persistence of the positive skin prick test (wheal area 30 mm^2) and of increased serum-specific IgE against ranitidine was documented.

This report presents two noteworthy findings. The first is that of the risk associated with intravenous ranitidine, and the second, that of the presence of specific IgE.

Ranitidine is a drug very commonly used intravenously in operating room, in surgical departments or intensive care units, and orally in medical departments; it has a good safety profile and the incidence of anaphylactic reactions is low in clinical practice (0.3%-0.7%) (5).

However, the intravenous infusion of ranitidine seems associated with the most severe allergic reactions (5), one of which was fatal (6).

Since our patient claims never having received ranitidine, we documented an anaphylaxis at first exposure for intravenous ranitidine.

Anaphylaxis at first exposure has been documented in particular for neuromuscular blocking agents (3, 8) but has also been reported for ranitidine (7). The origin of specific IgE involved in such reaction is unknown, the sensitising role of environmental agents has been speculated, but not firmly demonstrated (8).

The reliability of skin testing and detection of serum IgE detection through an allergological workup in patients with a positive case history for allergic side effects after ranitidine intake or other H2 receptor antagonists is disputed and the placebo controlled oral challenge test remains the golden standard (9).

However our study confirms the presence (10) and the persistence of specific IgE in ranitidine-induced anaphylaxis and highlights the ability of radioimmunoassay using epoxy-activated sepharose to detect specific IgE to small molecules (11, 12).

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References

1. Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative anaphylaxis. Med Clin North Am 2010; 94 (4): 761-89.
2. Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: post mortem findings and associated comorbid diseases. Ann Allergy Asthma Immunol 2007; 98: 252-7.
3. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: An 8-year national survey. J Allergy Clin Immunol 2011; 128(2): 366-73.
4. Baldo BA, Harle DG. Drug allergenic determinants. Monogr Allergy 1990; 28: 11-51.
5. Demirkan K, Bozkurt B, Karakaya G, Kalyoncu AF. Anaphylactic reaction to drugs commonly used for gastrointestinal system diseases: 3 case reports and review of the literature. J Investig Allergol Clin Immunol 2006; 16 (3): 203-9.
6. Oliva A, Partemi S, Arena V, et al. Fatal injection of ranitidine: a case report. J Med Case Reports 2008; 17; 2: 232.
7. Greer IA, Fellows K. Anaphalactoid reaction to ranitidine in labour. Br J Clin Pract 1990; 44 (2): 78.
8. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, et al. Hypersensitivity reactions to neuromuscolar blocking agents. Curr Pharm Des 2008; 14 (27): 2809-25.
9. Walker AI, Werfel S, Kick G, Przybilla B. Repeated anaphylactic responses induced by oral challenge with ranitidine. Acta Derm Venereol 2010; 90: 189.
10. Koh YI, Park HS, Choi IS. Ranitidine-induced anaphylaxis: detection of serum specific IgE antibody. Allergy 2006; 61: 269-70.
11. Campi P, Manfredi M, Severino MG. IgE-mediated allergy to pyrazolones, quinolones and other non-beta-lactam antibiotics. In: Pichler WJ editor. Drug Hypersensitivity. Basel: Karger; 2007: 216-232.