

## THE MOST COMMONLY IDENTIFIED CAUSE OF PERIOPERATIVE HYPERSENSITIVITY REACTIONS

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### ABSTRACT

**Introduction.** Perioperative anaphylaxis is a clinical condition that range from mild symptoms to life-threatening reactions. There is a geographic difference in the most frequent identified cause of perioperative drug hypersensitivity reactions. However, data from national surveys are lacking. **The aim** of this study was to evaluate the cause of perioperative drug hypersensitivity reactions among patients with a history of perioperative anaphylaxis. **Materials and Methods.** A total number of 195 patients [68(34.87%) men; mean age 57 years; SD 40.8; age range 10-79] with a history of perioperative anaphylaxis were included. All patients were referred in a specialized allergy centre for evaluation within at least six weeks of hypersensitivity reaction during anesthesia. Allergy evaluation included a detailed medical history, review of perioperative medical records and skin testing for all drugs and products administered during the anesthesia. Skin testing was performed with nonirritating concentrations. If the skin prick test was negative, intradermal test was performed, when available. **Results:** A culprit drug, defined as a positive skin test, was identified in 115(58.97%) patients. A total number of 111 patients had allergy to one agent and 4 – to two. The most common agents identified were neuromuscular blocking agents (NMBAs) – 68 positive skin tests in 61 (53.04%) patients. Reactions were as followed: pipecuronium -25(36.76%), rocuronium - 25(36.76%), suxamethonium - 13(19.12%), atracurium -5 (7.35%). Four patients had allergy to two NMBAs. Other identified agents were: fentanyl 10(8.7%), ketamine 13(11.3%), midazolam 11(9.57%), propofol 18 (16.65%), latex 2(1.74%).

**Conclusions:** The leading causes of perioperative anaphylaxis in our study population were NMBAs. More data from multicenter national surveys should be collected in future.

**key words:** *drug allergy; hypersensitivity; anesthesia; neuromuscular blocking agents*

### INTRODUCTION

Drug hypersensitivity reactions (DHRs) during anesthesia are unpredictable, dose-independent, noxious and unintended. Only when a definite immunological mechanism is demonstrated, these reactions should be classified as drug allergy. Several mechanisms are implicated, included IgE and non IgE mediated reactions. Immediate DHRs are possible induced by IgE-mediated mechanism and occur 2-6 hours after last drug administration. They usually manifest as isolated symptoms or as anaphylaxis [1]. Several drugs are often administered simultaneously during general anesthesia, making identification of the causative agents difficult. Identification of the culprit drugs of perioperative DHR is essential to avoid re-exposure and prevent subsequent untoward events [2]. Guidelines recommended comprehensive skin testing to all perioperative medications used during anesthesia and latex. The specific allergy work-up should be carried out four to six weeks after completed resolution of all clinical symptoms.

The incidence of allergic perioperative reactions have been estimated to occur in 1:3500 to 1:20000 procedures from different countries with a mortality rate of up to 9% [3]. The literature suggests that there is a geographic difference in the most frequently identified cause of

perioperative DHRs. The best data is from a French survey [4]. Studies from Europe have implicated neuromuscular blocking agents (NMBAs) whereas studies from the United States implicate antibiotics. [5,6]. However, data from national Bulgarian survey are lacking and can be useful in reducing the risk of anaphylaxis in patients who require subsequent anesthesia. **The aim** of this study was to evaluate the cause of perioperative drug hypersensitivity reactions on a number of Bulgarian patients.

## MATERIALS AND METHODS

### *Study design:*

This prospective study was conducted in the Allergy Unit of the University hospital “St. George”. It was designed to include patients, referred to specialized allergy centre for evaluation within at least six weeks of drug hypersensitivity reaction during anesthesia.

### *Patients:*

A total number of 195 patients with a history of perioperative anaphylaxis were included. Allergy evaluation included a detailed medical history, review of perioperative medical records and skin testing for all drugs and products administered during the anesthesia.

### *Skin testing:*

Skin testing was performed and evaluated with nonirritating concentrations as described by the European Academy of Allergy and Clinical Immunology position paper [7]. A positive skin prick test was defined by a wheal reaction  $\geq 3$  mm in diameter or of a size equal to or larger than the positive control (histamine) after 15 minutes. Saline 0.9% was used as a negative control. If the skin prick test was negative, intradermal test was performed, when available, defined as positive by wheal reaction  $\geq 7$  mm in diameter after 15 minutes (table 1).

**Table 1.**

## RESULTS

We evaluated 195 patients [68(34.87%) men; mean age 57 years; SD 40.8; age range 10-79]. The patients' demographic characteristics are presented in table 2.

**Table 2.**

A culprit drug, defined as a positive skin test, was identified in 115(58.97%) patients (fig. 1). A total number of 111 patients had allergy to one agent and 4 – to two (fig. 2). The most common agents identified were neuromuscular blocking agents (NMBAs) – 68 positive skin tests in 61 (53.04%) patients (fig. 3). Reactions were as follows: pipecuronium - 25(36.76%), rocuronium - 25(36.76%), suxamethonium - 13(19.12%), atracurium - 5 (7.35%). Four patients had allergy to two NMBAs. Other identified agents were: fentanyl 10(8.7%), ketamine 13(11.3%), midazolam 11(9.57%), propofol 18 (16.65%), latex 2(1.74%) (fig. 4).

**Figure 1.**

**Figure 2.**

**Figure 3.**

**Figure 4.****DISCUSSION**

A hundred and ninety five patients completed a comprehensive evaluation after a perioperative anaphylaxis. Positive akin test, which identified IgE mediated HDRs was established in 115 (58.97%) patients. Our results were similar to other publications. Dong et al. in France, evaluated 1,253 patients with HSR during anesthesia, and were able to establish a diagnosis of IgE-mediated HSR in 786 cases (63%) while 467 cases (37%) were considered non-immune-mediated [8]. Our results demonstrated that HDRs were more common in women compared to men. It has been hypothesized that the increased incidence of immediate hypersensitivity in women would be due to a possible cross-sensitization with quaternary ammonium ion-containing compounds such as cosmetics and other personal care products [4]. However, this hypothesis is not yet confirmed.

We identified NMBAs as the most commonly identified cause of perioperative HSRs by skin testing. This observation is important since data have varied between studies and countries. The French investigators demonstrated that NMBAs were the most frequent cause of anaphylaxis (47%), followed by latex (20%), antibiotics (18%), opioids (2%), colloids (2%), hypnotics (1%), and other substances including dyes (9%) [8]. In the United States, preoperative antibiotics is the most common cause of perioperative anaphylaxis, accounting for 50% of IgE-mediated reactions, compared with France, where it makes up only 12% to 15% of cases [9]. A study from Spain reported a much higher incidence of antibiotics causing anaphylaxis (44%) [10].

Antibiotics were not identified as culprit drugs in our study. More than half of the patients - 53.04% were sensitized to NMBAs. We confirmed that rocuronium was among the most commonly implicated NMBAs. The frequency of sensitization to rocuronium and pipecuronium was the highest and similar. We did not confirm high prevalence of sensitization to suxamethonium, published in another studies [11, 12]. Our observations are important from practical point of view. IgE sensitization may persist for years, as shown for MNBAs. Expert therefore recommended lifelong avoidance of the drug and cross-reactive drugs when drug-induced anaphylaxis has occurred [1]. Corticosteroids and H1-antihistamines may not reliably prevent Ig-E dependent anaphylaxis.

Four patients in our study had allergy to two NMBAs. Cross-reactivity has been documented among NMBAs [3]. That is why it is important for patient with a reaction to NMBAs to use alternative agents. Skin test to several NMBAs agents is essential.

It was interesting for us to identify only two patients (1.74%) were sensitized to latex. Historically, latex accounted for approximately 20% of perioperative anaphylaxis cases [4]. However, the incidence of latex allergy has decreased because of primary prevention measures such as the use of powder-free latex gloves and nonlatex surgical material) in the operating room.

**CONCLUSION**

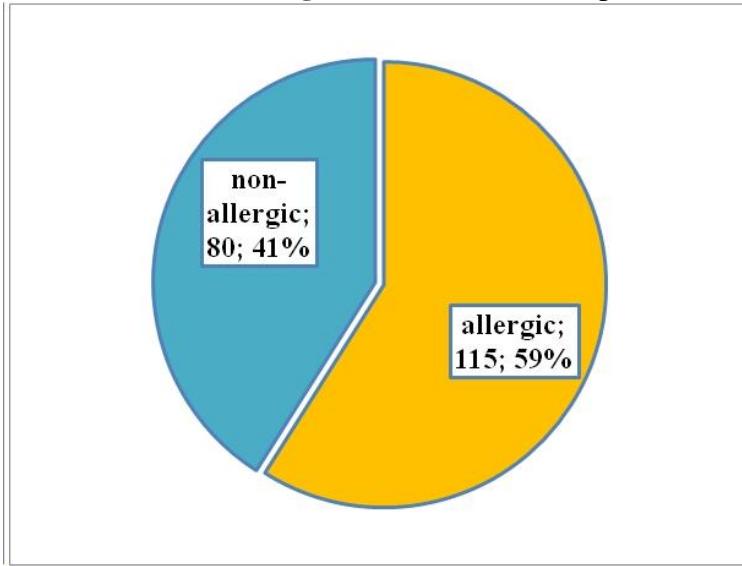
The leading causes of perioperative anaphylaxis in our study population were NMBAs. More data from multicenter national surveys should be collected in future.

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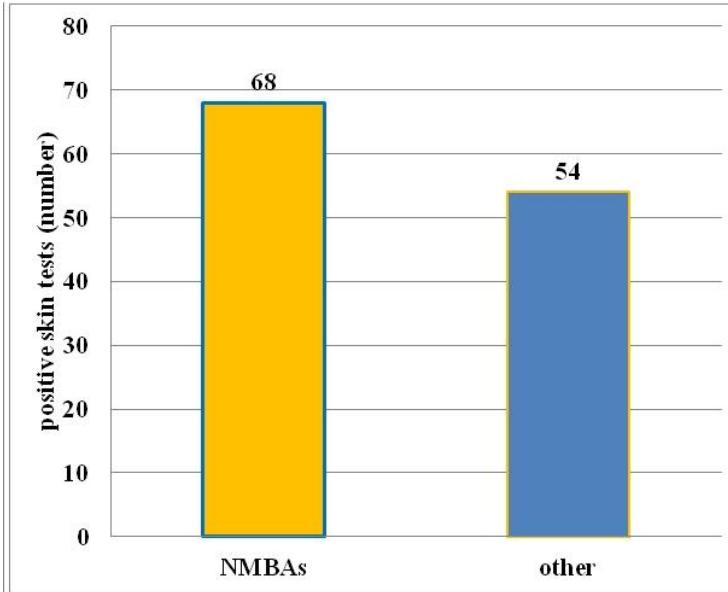
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**LEGENDS TO FIGURES:**

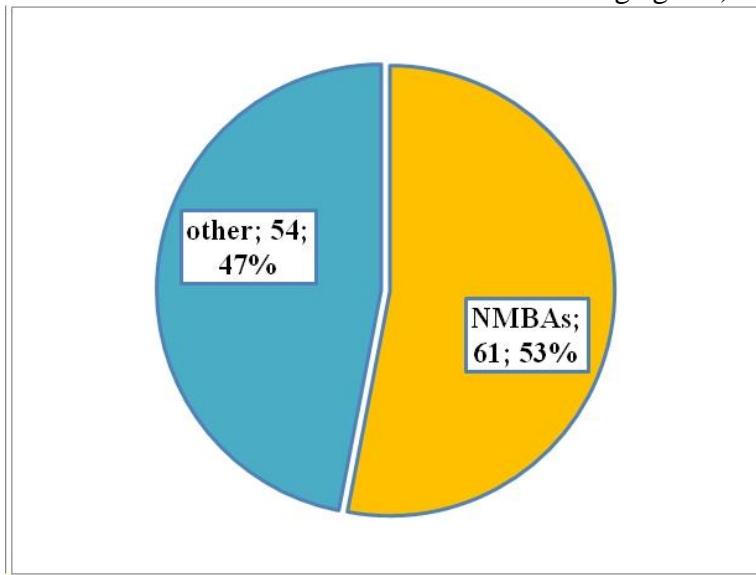
**Figure 1.** Distribution of patients on the base of allergy



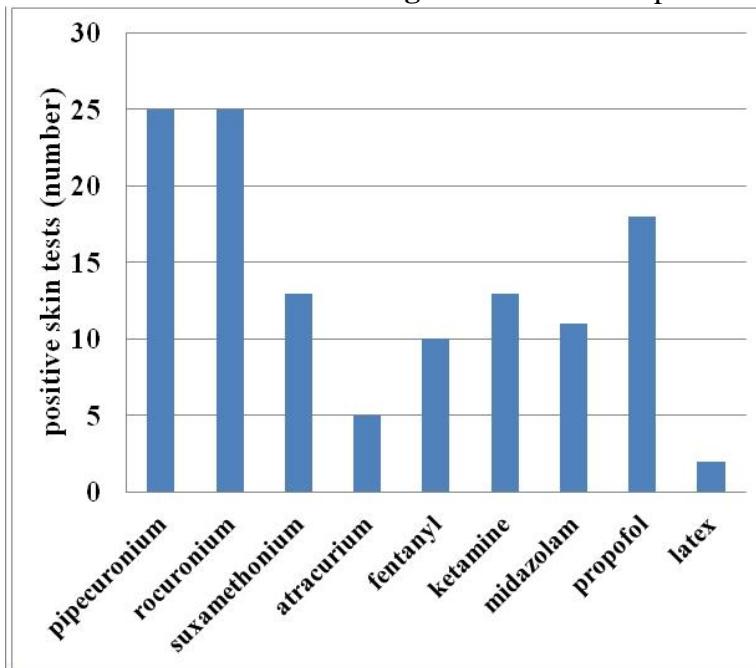
**Figure 2.** Patients with positive skin tests / (NMBAs - neuromuscular blocking agents).



**Figure 3.** Distribution of patients with positive skin tests / (NMBAs - neuromuscular blocking agents).



**Figure 4.** Number of positive skin tests



Nonirritating test concentrations for perioperative drugs.

**Table 1.**

Drug	Undiluted concentration (mg/ml)	SPT dilution (maximum concentration mg/ml)	IDT dilution (maximum concentration mg/ml)
Suxamethonium	50	1/5 (10)	1/500 (0.1)
Rocuronium	10	Undiluted	1/200 ((0.05)
Pipecuronium	1	Undiluted	NA
Atracurium	10	1/10 (1)	1/1000 (0.01)
Fentanyl	0.05	Undiluted	1/10 (0.005)
Ketamine	10	Undiluted	1/10 (1)
Midazolam	5	Undiluted	1/10 (0.5)
Propofol	10	Undiluted	1/10 (1)
Thiopental	25	Undiluted	1/10 (2.5)
Latex			
SPT – skin prick test; IDT – intradermal test; NA – not available			

Patients: characteristics.

**Table 2.**

Gender:	
male	68 (34.87 %)
female	127 (65.13%)
total	195
Age:	
mean (SD)	56.76 (40.8)
age range	10 – 79