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Hypersensitivity Reactions During Anaesthesia Care: An 11-Year Experience From A Tertiary Hospital

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Abstract

Introduction: Anaphylaxis during general anaesthesia is a rare but life-threatening clinical condition involving multiple organ systems, with a reported incidence of 1 in 4.000 to 25.000 anesthetic procedures. The objective of this study is to describe the experience of a Tertiary University Hospital with drug hypersensitivity reactions, including anaphylaxis, during anaesthesia care, their main causal agents, treatment and investigation.

Methods: All patients submitted to surgical interventions under anaesthesia, between 2006 and 2016, with the coded diagnosis of perioperative anaphylactic reaction were retrospectively reviewed. Data was collected from clinical records. Those without a full record were excluded. Demographic data, causal agents, presenting symptoms and treatments were gathered. Perioperative anaphylaxis was graded using the Ring and Messmer system. Whenever available, serum Tryptase levels were registered. A descriptive analysis of the data was performed.

Results: 67 patients had the diagnosis of anaphylaxis in a perioperative setting. Of the 62 included, 59,7% were males with median age of 57 years old. The culprit drugs were identified in 82,2% of the patients, and were mainly neuromuscular blocking agents, antibiotics and contrast agents. 40,3% had a grade 1 reaction and 30,2% a grade 2. The anaphylaxis was mostly treated with corticosteroids and antihistamines. Twelve patients needed intensive care stay, and one patient died. Seven patients were referenced to an Immunology consultation. Tryptase measurements were available for 13 patients (20,9%). Of those, four had elevated levels.

Discussion and conclusion: Hypersensitivity reactions during anaesthesia had an incidence of 1 in 3.000, and NMBAs and antibiotics were the main causal agents. Although most of the reactions were graded 1 or 2, there was still a significant number with major clinical importance. The non-uniform pharmacologic approach and the lack of follow-up by an Immunology team are points of improvement in the care of these patients.

Keywords: Anaphylaxis; Hypersensitivity reaction; Drugs; Anaesthesia; Serum tryptase

Introduction

Drug hypersensitivity reactions that occur during anesthesia are responsible for significant morbidity, mortality and socio-economic costs. The reaction may be allergic or anaphylactoid. The former result from the presence of allergen specific IgE (or IgG) antibodies. The latter may be related to other mechanisms, such as complement activation, histamine release or activation of the mast-cell specific MRGPRX2 receptor, or even unknown mechanisms [1,2]. Anaphylaxis is considered an acute type I hypersensitivity reaction resulting primarily from rapid antigen induction. Anaphylaxis during general anaesthesia is a rare but life-threatening clinical condition involving multiple organ systems, and this terminology is usually used when the allergic reaction is associated with cardiovascular collapse or airway obstruction, with or without cutaneous manifestations [3]. Epidemiological studies report a variable incidence of one allergic reaction in 4.000 to 25.000 anesthetic procedures, with overall mortality rate ranging from 0.001% to 9% [1,4-9].

Although clinical judgment is essential to the research of the causal agent, during an anesthetic induction several drugs are used almost simultaneously which makes this finding harder to achieve. Immunology and Allergology tests and follow-up are, therefore, of major importance to the investigation of the patients [6,9,10].

The main purpose of this study is to describe the experience of a Tertiary University Hospital with drug hypersensitivity reactions, including anaphylaxis, during anaesthesia care, their main causal agents, treatment and investigation, and compare data from our center with others.

Methods

After approval from the Hospital's Ethics Committee, all patients submitted to surgical interventions under anaesthesia between 2006 and 2016 with the coded diagnosis of perioperative anaphylactic

reaction, according to the ICD-9 classification, were retrospectively reviewed.

The data was collected from clinical records. Patients without a full record were excluded. Demographic data, American Society of Anesthesiologists (ASA) score, causal agents, presenting symptoms and treatments were collected. The severity of the drug reaction was graded using the Ring and Messmer criteria, which divides these reactions in grade 1: generalized skin symptoms; grade 2: mild to moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms; grade 3: life threatening symptoms; grade 4: cardiac and/or respiratory arrest [11,12]. Whenever available, serum tryptase levels and serum IgE levels were registered.

A descriptive analysis of the data was performed using SPSS version 23.0 (SPSS Inc.,Chicago, Illinois).

Results

During the period from January 2006 to December 2016, 216.307 surgical interventions were carried out under anaesthesia in our hospital, both in the operating room and in non-operating room settings. A total of 67 patients had a codification of the diagnosis of anaphylactic reaction in a perioperative setting, which counts for an incidence of 1:3.000 patients.

Five patients were excluded from the study for lack of information in the clinical records. Of the 62 included, 25 (40.3%) were females and 37 (59.7%) males, and the median age was 57 years old (minimum 4 years old, maximum 88 years old). Most patients were ASA II (43.5%) (Table 1).

General Data	
Age	57 (4-88)
Gender	
Male	37 (59.7%)
Female	25 (40.3%)
ASA Score	
I	12 (19.4%)
II	27 (43.5%)
III	18 (29.0%)
IV	5 (8.1%)

Table 1: Demographic data; n (%).

Nine patients (14.5%) had a previous allergy history. Five of them had history of allergic reaction to beta-lactamase antibiotics, and the remaining ones had a previous reaction to contrast medium, aspirin, iodopovidone and pollens.

In 51 patients (82.2%) the culprit drugs were identified, mostly by association with the timing of the drug administration and the beginning of the symptoms. Table 2 sums up the suspected agents. Neuromuscular blocking agents (NMBAs) were the most common drugs, with a total of 14 events (22.6%). Overall, 11 (17.7%) patients had an allergic reaction to rocuronium, two to atracurium and one patient to cisatracurium. Antibiotics were also quite common agents, with eight (12.9%) reactions to beta-lactamic antibiotics, mainly cephazolin and cephoxitin, three reactions to vancomycin and one reaction to gentamicin. The remaining causal drugs were contrast agents, propofol, fentanil, ranitidine, fresh frozen plasma, adhesive, intravenous iron, octreotide and paracetamol.

Allergens	
Unknown	11 (17.7%)
Rocuronium	11 (17.7%)
Beta-lactamics	8 (12.9%)
Contrast medium	6 (9.7%)
Propofol	6 (9.7%)
Ranitidine	5 (8.1%)
Vancomicin	3 (4.8%)
Atracurium	2 (3.2%)
Fentanil	2 (3.2%)
Fresh Frozen Plasma	2 (3.2%)
Adhesive	1 (1.6%)
Cisatracurium	1 (1.6%)
Intravenous Iron	1 (1.6%)
Gentamicin	1 (1.6%)
Octreotide	1 (1.6%)
Paracetamol	1 (1.6%)

Table 2: Suspected allergens; n (%).

Considering the severity of the clinical reaction, 40.3% of the patients had a grade 1 reaction, presenting only cutaneous symptoms such as generalized erythema. A total of 30.6% had a grade 2 reaction, with laryngospasm, hypotension and edema of the airway requiring an advanced airway. Patients with a grade 3 reaction (25.8%) presented more severe cardiopulmonary symptoms. Two patients were classified with grade 4 reaction, both presented with immediate cardiopulmonary arrest, and one of them died in the intensive care unit (Table 3).

Classification of the reaction	
Grade 1	25 (40.3%)
Grade 2	19 (30.6%)
Grade 3	16 (25.8%)
Grade 4	2 (3.2%)

Table 3: Classification of the reaction; n (%).

The anaphylactic reactions were mostly treated with corticosteroids (hydrocortisone) and antihistamines (clemastine). According to hospital records, adrenaline was used in 10 patients (16.1%).

Most patients went directly to the ward after the surgical procedure (n=40; 64.5%), and two patients who had day surgery where

discharged on the same day (3.2%). Meanwhile, 12 went to an intensive care unit (19.4%) and eight to an intermediate care unit (12.9%). The median length of hospital stay was four days (0; 52).

Seven (11.3%) were referenced to an Immunology and Allergology consultation in our hospital. Data from referencing to other hospitals was not available. Tryptase measurements were available for 13 patients (20.9%) (Table 4). Of those, four patients had elevated levels in the first hours after the hypersensitivity reaction (>13.5 µg/L). The remaining seven patients had normal levels and two of them had elevated levels for more than 24 h after the event. IgE measurements were available for 11 patients, with only four having elevated levels. Skin tests were performed in the seven patients with follow-up consultation, and in 2 of them Basophil Activation Tests were made, with positive results.

	Tryptase measurements		
Type of reaction	1st sample	2nd sample (1-2 h)	3rd sample (>24 h)
3			74.6
3			10.3
3			66
2			5.31
3		93.6	
2		1.74	
3		6.1	2.5
2	30.5	21.2	2.5
3	2.8	2.68	1.77
2		190	
4		6.22	8
3		6.15	5.52
3	20.8		6.15

Table 4: Tryptase measurements (ug/L). Normal <13.5.

Discussion

Reports in the literature of the incidence of anaphylactic reactions in the operating room are variable, but in our Centre this incidence seems to be greater than the one reported in other similar studies [1]. There might be an over-report of anaphylactic reactions, for which we point out several reasons. The codification for anaphylactic reaction in our Hospital involves all hypersensitivity reactions, related or not to the presence of allergen specific IgE antibodies. Also, an important percentage of the identified patients had a grade 1 reaction, which is not considered anaphylaxis since it only involves cutaneous symptoms. The lack of patient follow-up also limits the precise diagnosis with the appropriate immunologic testing.

The most common agents responsible for the described hypersensitivity reactions in a perioperative setting were NMBAs, mainly rocuronium, immediately followed by antibiotics, especially cephazolin and cephoxitin, which are also the most frequently used for preoperative prophylaxis. These results are similar to previous studies, in which the main agents involved in IgE-mediated perioperative anaphylaxis were neuromuscular blocking agents, latex, antibiotics, hypnotics, opioids, and colloids [7,13,14]. In the United States, antibiotics, contrary to NMBAs, were the most common identifiable cause of Perioperative Anaphylaxis [15,16].

There were no latex allergies reported during the period of the study, which could be due to underreport but could also be associated with the higher frequency of previous diagnosis of this reaction since latex is often found in every-day materials, outside the operating room. Furthermore, the existing protocol for patients with known latex allergy is very well establish which helps to prevent these complications. Reactions to latex are rapidly decreasing in other studies, as a result of primary and secondary prevention policies [1].

The culprit drugs were identified in 82.2% of the patients. Association with the timing of the drug administration and the beginning of the symptoms deduced most of the causal agents. This is a suboptimal way of determining the responsible drugs, since during anesthesia, several drugs are administered in consecutive moments. There are also other factors that mimic the clinical picture of anaphylaxis, including direct mast cell mediator release and other causes of hypotension and bronchospasm, including the pharmacological action of the anesthetic drugs themselves [17].

The importance of follow-up and specific testing resides in this difficulty, and is necessary for avoiding potential re-exposure of the patients to the offending drugs. Specific investigation should therefore be conducted 4 to 6 weeks after the reaction and relies on skin tests, serum-specific IgE, and challenge procedures [1,4].

Determination of mast cell Tryptase can be useful in the discrimination of IgE and non-IgE-mediated reactions [18]. The presence of this enzyme is therefore a key element in diagnosing anaphylactic reactions [19]. However, the optimum number of Tryptase measurements and the best interpretative strategy has not yet been established in perioperative anaphylaxis [20-22]. Our internal protocol for Anaphylaxis in the perioperative period includes a proposal for Tryptase measurements. The first sample is collected immediately after resuscitation, the second sample in the 1-2 h following the hypersensitivity reaction (maximum 6 h), and the third sample, which corresponds to the basal levels of Tryptase, should be collected more than 24 h after the reaction, or even during the immunoallergology consultation. Despite the existing protocol, there was a considering lack of follow-up of patients after Anaphylaxis in the operating room. Of the 11 patients with Tryptase measurements, only three had their samples collected immediately after the reaction. Of these, two patients had Tryptase values that suggested anaphylactic reaction, while the third patient had no increase in Tryptase levels. Four patients had their samples taken later, presenting high values, which call for a revaluation by the Imunoallergologist and further testing to exclude the differential diagnosis of Mastocitosis. The remaining patients didn't have their samples collected in the proper timing, and therefore no conclusions can be extracted from their results.

Of patient risk factors, a study conducted in the University of Michigan Hospital, only personal history of anaphylaxis was associated with an increased risk of hemodynamic significant anaphylaxis [23]. In our study, no patient had a previous history of anaphylaxis, and only nine patients had a previous allergy history.

Considering the severity of the hypersensitivity reactions, 40,3% of the reactions had a grade 1 classification. These reports were of simple

cutaneous reactions, some of them localized, which might suggest only a histamine mediated reaction associated with drugs like rocuronium, ranitidine, opioids, or even anxiety. Meanwhile, 25,8% of the patients had a grade 3 reaction with important hemodynamic and respiratory consequences, and two entered cardiorespiratory arrest. Since anaphylaxis presents with significant hypovolemia and vasoplegia, aggressive fluid therapy and adrenaline are the cornerstones of management [10]. Despite this fact, in our study adrenaline was only given in 10 patients.

This study describes the experience of a Portuguese Tertiary Hospital with perioperative hypersensitivity reactions, including anaphylaxis. Our results confirm an increased incidence in comparison to other studies, which is a matter to be addressed in the future. The proper follow-up of these patients must also be improved, with better communication between the Departments of Anaesthesiology and Immunology. A protocol for the treatment of these situations has already been created, and includes specific postoperative tests and follow-up, but its implementation is lacking. It is therefore important to renew the information about this topic in our hospital and to re-educate all the involved professionals.

Conclusion

The incidence of perioperative hypersensitivity reactions was 1:3000, higher than the ones reported in previous studies. Our results confirm that neuromuscular blocking agents and antibiotics remain the main causal agents of perioperative anaphylaxis in anaesthesia care. Although most of the reactions were graded 1 or 2, and didn't need any specialized care afterwards, there was still a significant number with major clinical importance. The non-uniform pharmacologic approach and the lack of follow-up by an Immunology and Allergology team are points of improvement in the care of these patients.

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