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The cause of perioperative hypersensitivity in adults and consequences of subsequent anesthesia

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Abstract
Background: In the perioperative period, patients are exposed to many agents that may cause hypersensitivity reaction; so, finding the culprit drug is important for patient safety in the event of the need for repeat anesthesia.
Aim: Our aim was to share demographic data, clinical features, and diagnostic tests of patients who developed perioperative hypersensitivity (POH) and in whom the culprit drug was identified.
Methods: Patients evaluated for POH between 2016 and 2024 were retrospectively analyzed. Results of anesthesia notes, agents used in anesthesia, skin prick test, and intradermal test (IDT) to determine the culprit drug were examined. Patients were interviewed by telephone and questioned about their reanesthesia status.
Results: The files of 167,688 patients were analyzed; 405 patients were referred and tested for POH and 330 patients were excluded from the study because they had no history of POH or the culprit drug could not be identified. The study was completed with 75 patients. POH developed during the induction of anesthesia (I) in 18, maintenance (M) in 34, and at the end (E) in 23 patients. The median age was 48, out of which 89.3% (n = 67) were females. Reactions developed during genitourinary system surgery in 33.3% (n = 25), ear-nose-throat surgery in 17.3% (n = 13), and abdominal surgery in 17.3% (n = 13); anaphylaxis developed in 56% (n = 42) (I: 9; M: 21; E: 12); cutaneous involvement in 73.3% (n = 55); cardiovascular

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involvement in 41.3% (n = 31), respiratory system involvement in 56% (n = 42), and gastrointestinal involvement in 4% (n = 3); Brown grade 1 in 44% (n = 33) and grade 3 in 38.7% (n = 29); Ring and Messmer classification, grade 1 in 44% (n = 33); and cardiac arrest in five patients. For the distribution of culprit drugs: neuromuscular blocking agents (NMBAs) in 22.7%, opioids in 21.4%, hypnotics in 17.3%, and antibiotics in 14.6%. In four patients, multiple agents were determined. Skin prick test was positive in 35.1% and IDT positivity was found in 98.6%. Surgery was cancelled in 40% (n = 30), but it was determined that 50 patients (66.7%) underwent surgery after drug tests. All of them tolerated surgery.

Conclusıon: A large number of patients were evaluated because we are a reference hospital. The most common culprit drug group in POH is NMBA; reanesthesia situations are safe after allergist evaluation.

Introduction

In the perioperative period, patients are exposed to many agents that may cause hypersensitivity reaction.[1,2] Although it is mentioned that the incidence is low in retrospective studies, it is noteworthy that it is higher in prospective studies. In a prospective study conducted in Spain, the incidence was calculated as induction of anesthesia (I): 381; only skin involvement was observed in 48% of patients with hypersensitivity and anaphylaxis observed in 52%.[3]

In patients who develop perioperative hypersensitivity (POH), a detailed anamnesis should be obtained and the anesthesia file should be examined. Anesthetist notes of hypersensitivity reactions should be examined and examination findings in the patient should be evaluated. Skin test with the drugs used in the operation is recommended.[4] Finding the culprit drug is important for patient safety in the event of the need for repeat anesthesia.[5]

Here, we describe a retrospective of a large reference center experiences, including all patients with POH reactions and tested between January 01, 2016, and May 31, 2024.

Methods

Study population and data collection

Patients who were referred to our tertiary outpatient clınıc (Department of Allergy Immunology at University of Health Sciences, Süreyyapaşa Training and Research Hospital) with a history of drug allergy were retrospectively screened. (A total of 167,688 patients were evaluated in the outpatient clinic; 405 patients were evaluated for POH.) Patients in whom the culprit drug could not be determined by diagnostic tests and patients with no previous history of POH were excluded from the study; 75 patients were included in the study (0.044%) and anesthesia records and allergy tests of the patients were examined.

A standardized patient record form was filled for each patient. Demographic data (age, gender), allergic characteristics (atopy, allergic comorbidities, other drug allergy), and severity of POH (Ring and Messmer; Brown classification),[4,6] systems affected in POH were analyzed. Latex-specific immunoglobulin E (IgE) is sometimes tested in our hospital. If available, specific IgEs > 0.35 kU/L were accepted as positive (ImmunoCAP, Thermo Scientific).[7] All patients underwent the skin prick test and intradermal test (IDT) with suspected agents. IDT was performed if the skin prick test was negative or suspicious. Skin prick test and IDT doses for all drugs were performed at the concentrations specified in the European Academy of Allergy and Clinical Immunology (EAACI) position paper.[4]

As mentioned in the study by Horiuchi et al., the timing of the onset of symptoms was examined in three categories: induction, maintenance, and end of anesthesia. The induction of anesthesia is 10 minutes after the onset of anesthesia. End of anesthesia is the time between the end of surgery and the end of anesthesia. Maintenance is the time between induction and end.[8]

After the test results, the patients were informed about alternative agents responsible for POH. After the file reviews were completed, the patients were called and questioned about their reoperation status and whether they had POH.

Ethics Committee approval was obtained prior to the study at the University of Health Sciences, Süreyyapaşa Training and Research Hospital (116.2017.R-295).

Statistical analysis

The data obtained from the study were transferred to the computer and analyzed with SPSS (Statistical Package for Social Sciences) 25.0 package program. In descriptive analyses, frequency data were given as number (n) and percentage (%) and numerical data were given as arithmetic median (IQR). Pearson's chi-squared test was used to compare categorical data. The compatibility of the numerical data with normal distribution was analyzed by the Kolmogorov-Smirnov and Shapiro Wilk tests. The distribution of non-normal distributed numerical data in more than two independent groups was analyzed by the Kruskal Wallis test.

ROC (Receiver Operating Characteristics) Curve Analysis was used to predict perioperative hypersensitivity. Binary Logistic Regression and multinominal logistic regression

analysis were used to predict the risk of perioperative hypersensitivity.

Statistical significance was accepted as $p < 0.05$ for all tests.

Results

Characteristics of the study population

Ours is a reference hospital where many patients are referred for evaluation for drug allergy. In our center, 405 patients were referred and tested for POH; 330 patients were excluded from the study because they had no history of POH or the culprit drug could not be identified. The study was completed with 75 patients (Figure 1**).**

The severity of the POH, culprit drugs, comorbidity

It was determined that the reaction developed during induction of anesthesia in 18, maintenance in 34, and at the end in 23 patients. The distribution of demographic and clinical characteristics of the patients according to the time of reaction is presented in Table 1**.**

The median age of all patients was 48 (33-59) years and there was no statistical difference in the distribution of age according to reaction time ($p = 0.556$). Of all patients, 89.3% (n = 67) were female. A history of atopy was recorded in 32.0% (n = 24), asthma in 22.7% (n = 17), and allergic disease in 43.2% (n = 32) in all the patients.

There was no statistical difference in the distribution of asthma, atopy, and allergic disease history rates according to the time of reaction development ($p > 0.05$). It was determined that 42.7% of patients had a history of drug allergy before POH and no statistical difference was determined in the distribution of this rate according to the time of reaction development ($p = 0.782$). Reactions developed during genitourinary system surgery in 33.3% (n = 25), ear-nose-throat surgery in 17.3% (n = 13), and abdominal surgery in 17.3% (n = 13) of the patients. Laboratory parameters such as eosinophil, neutrophil, lymphocyte, total IgE, and tryptase levels were statistically similar according to the time of reaction development ($p > 0.05$).

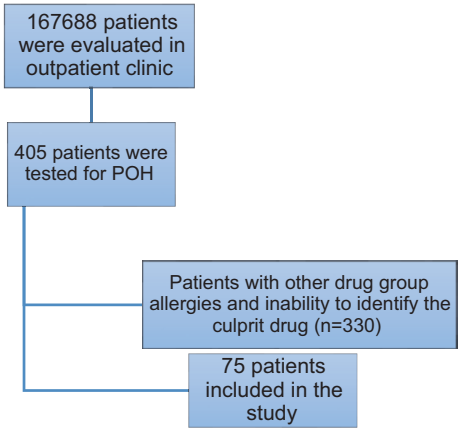

Figure 1 Study population.

The distribution of reaction characteristics according to the time of POH is presented in Table 2.

The number of previous general anesthesia was 1 (1-1). There was no statistical difference in the number of previous general anesthesia according to the time of POH ($p = 0.173$). Anaphylaxis developed in 56% of patients (n = 42), in 50% with induction, in 61.8% with maintenance, and in 52.2% at the end; cutaneous involvement was observed in 73.3%, cardiovascular involvement in 41.3%, respiratory system involvement in 56%, and gastrointestinal involvement in 4% **(**Figure 2**).** There was no statistical difference in the distribution of system involvement according to the time of POH ($p > 0.05$).

When analyzed according to Brown classification, grade 1 reaction was observed in 44% (n = 33) and grade 3 in 38.7% (n = 29). According to Ring and Messmer classification, grade 1 was observed in 44% (n = 33) and cardiac arrest was recorded in five patients. Short-acting antihistamine + methylprednisolone was given most frequently with 61.2% (n = 30) in the treatment of reactions.

When the distribution of culprit drugs from POH was evaluated, it was determined neuromuscular blocking agents (NMBAs) (22.7%), followed by opioids (21.4%), hypnotics (17.3%), and antibiotics (14.6%). In four patients, multiple agents were determined **(**Figure 3**).** Skin prick test was positive in 35.1% of the patients. There was no difference in the distribution of skin prick test positivity according to the time of POH ($p = 0.583$). IDT positivity was found in almost all patients (98.6%). Surgery was cancelled in 40% (n = 30) of all patients, where the cancellation was highest in patients who developed maintenance POH ($p = 0,001$). The distribution of system involvement, skin prick test, and IDT positivity according to the time of POH is shown in Table 2**.**

In the binary logistic and multinominal logistic regression analyses performed with the data for POH, no appropriate risk factor could be identified. ROC analysis was performed for the cut-off point determination analysis of laboratory parameters for POH, but no statistically significant cut-off point was detected.

Surgery after drug tests

It was determined that 50 patients (66.7%) underwent surgery after drug tests. All of them tolerated surgery.

The data of 75 patients included in the study due to POH are presented in Table 3**.**

Discussion

In this study, demographic and clinical characteristics of patients who were evaluated for POH and in whom the culprit drug was identified were analyzed in detail. The main aim of our study was to present a comprehensive retrospective analysis of POH in an outpatient population in our tertiary referral hospital. Data on this subject in adult patients are limited in Türkiye. Identifying the culprit drug is very important for the safety of the patient, especially

Table 1 Distribution of Demographic and Clinical Characteristics by Time of POH.

	All patients (n=75)	Induction (n=18)	Maintenance (n=34)	End (n=23)	p
Age (year); [Median (IQR)]	48 (33-59)	50 (36-62)	47 (33-59)	45 (31-55)	0,556*
Gender (Female); [n (%)]	67 (89,3)	18 (100,0)	29 (85,3)	20 (87,0)	-
Atopy; [n (%)]	24 (32,0)	6 (33,3)	9 (26,5)	9 (39,1)	0,598**
Asthma; [n (%)]	17 (22,7)	3 (16,7)	6 (17,6)	8 (34,8)	0,249**
Allergic disease; [n (%)]	32 (43,2)	6 (33,3)	15 (45,5)	11 (47,8)	0,612**
Allergic disease					
Asthma	6 (18,6)	-	2 (13,3)	4 (36,4)	-
Rhinitis	9 (28,1)	2 (33,3)	5 (33,3)	2 (18,2)	
Asthma+Rhinitis	8 (25,0)	2 (33,3)	3 (20,0)	3 (27,3)	
Urticaria	4 (12,5)	1 (16,7)	2 (13,3)	1 (9,1)	
Urticaria+Angioedema	2 (6,3)	-	2 (13,3)	-	
Asthma + Urticaria	1 (3,1)	-	-	1 (9,1)	
Asthma + Urticaria + Rhinitis	2 (6,3)	1 (16,7)	1 (16,7)	-	
History of drug allergy before POH; [n (%)]	31 (42,7)	7 (38,9)	15 (47,1)	9 (39,1)	0,782**
History of drug allergy before POH					-
Antibiotics	6 (18,8)	1 (14,3)	3 (18,8)	2 (22,2)	
NSAID	4 (12,5)	1 (14,3)	1 (6,3)	2 (22,2)	
Multiple groups	19 (59,4)	5 (71,4)	9 (56,3)	5 (55,6)	
Local anaesthetic	2 (6,3)	-	2 (12,5)	-	
Operatıon Sıtes; [n (%)]					-
Ear-Nose-Throat surgery	13 (17,3)	4 (22,2)	4 (11,8)	5 (21,7)	
Genitourinary system surgery	25 (33,3)	6 (33,3)	11 (32,4)	8 (34,8)	
Dental treatment	3 (4,0)	-	3 (8,8)	-	
Abdominal surgery	13 (17,3)	3 (16,7)	6 (17,6)	4 (17,4)	
Endoscopy/colonoscopy	5 (6,7)	1 (5,6)	3 (8,8)	1 (4,3)	
Torax surgery /bronchoscopy	2 (2,7)	1 (5,6)	1 (2,9)	-	
Ophthalmic surgery	1 (1,3)	-	1 (2,9)	-	
Orthopedic surgery	9 (12,0)	2 (11,1)	5 (14,7)	2 (8,7)	
Cardiac surgery	2 (2,7)	-	-	2 (8,7)	
Breast surgery	2 (2,7)	1 (5,6)	-	1 (4,3)	
Eosinophil Count; [Median (IQR)]	100 (50-150)	100 (80-120)	100 (50-150)	65 (2-160)	0,394*
Eosinophil percentage; [Median (IQR)]	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0,961*
Neutrophil count; [Median (IQR)]	4570 (3427-6052)	4900 (3090-5190)	4300 (3440-6110)	4665 (3617-6390)	0,892*
Neutrophil percentage; [Median (IQR)]	60 (52-66)	54 (47-63)	61 (54-69)	59 (53-67)	0,073*
Lymphocyte count; [Median (IQR)]	2150 (1767-2787)	2700 (2160-3070)	1920 (1770-2470)	2270 (1512-3230)	0,170*
Lymphocyte percentage; [Median (IQR)]	31 (26-35)	32 (27-44)	30 (23-34)	31 (24-35)	0,503*
Total IgE; [Median (IQR)]	55 (51-152)	23 (18-67)	61 (27-192)	66 (29-323)	0,187*
Tryptase; [Median (IQR)]	4 (3-7)	6 (4-7)	3 (3-6)	4 (3-4)	0,212*

*: Kruskal Wallis Testi.
**: Pearson Ki-kare Testi.

when reanesthesia is required. Performing diagnostic drug tests in the patient with POH is the basis of medicine. This principle is "PRIMUM NON NOCERE."[9]

Türkiye is at the junction of Asia and Europe, where studies on POH in the adult age group are limited. The incidence of POH is quite low. In Japan, 70,523 surgeries from 56 centers were examined; perioperative anaphylaxis was seen in seven patients. The incidence was calculated as 0.010%.[10]). In our study, 167,688 patients' files were analyzed. Although 405 patients were tested for POH, POH was detected in 75 patients. The incidence of POH was calculated as 0.044%. Perioperative anaphylaxis was seen in 42 patients. The incidence of perioperative anaphylaxis was 0.025%.

Considering 330 out of 405 patients, it is noteworthy that most of the patients with suspected POH were not true POH. Similarly, Elmitwalli et al. mentioned mostly drug side effects and other nonallergic concerns.[11] Incorrectly

Table 2 The distribution of reaction characteristics according to the time of POH.

	All patients (n=75)	Induction (n=18)	Maintenance (n=34)	End (n=23)	p
POH development time/month; [Median (IQR)]	72 (28-144)	72 (27-144)	66 (27-231)	75 (24-144)	0,906*
Number of previous general anaesthesia; [Median (IQR)]	1 (1-1)	1 (1-2)	1 (1-1)	1 (1-1)	0,173*
POH reactıons; [n (%)]					
Urticaria	30 (40,0)	9 (50,0)	12 (32,3)	9 (39,1)	-
Urticaria+Angioedema	3 (4,0)	-	1 (2,9)	2 (8,7)	
Anaphylaxis	42 (56,0)	9 (50,0)	21 (61,8)	12 (52,2)	
Cuteneous Signs; [n (%)]	55 (73,3)	13 (72,2)	23 (67,6)	19 (82,6)	0,453**
Cardiovascular Signs; [n (%)]	31 (41,3)	9 (50,0)	17 (50,0)	5 (21,7)	0,072**
Respiratory Signs; [n (%)]	42 (56,0)	9 (50,0)	21 (61,8)	12 (52,2)	0,651**
Gastrointestinal Signs; [n (%)]	3 (4,0)	-	1 (2,9)	2 (8,7)	-
Brown Classification; [n (%)]					
Grade 1	33 (44,0)	9 (50,0)	13 (38,2)	11 (47,8)	-
Grade 2	13 (17,3)	1 (5,6)	6 (17,6)	6 (26,1)	
Grade 3	29 (38,7)	8 (44,4)	15 (44,1)	6 (26,1)	
Ring Messmer Grade; [n (%)]					
Grade 1 (Skin lesions and/or slight increase in body temperature)	33 (44,0)	9 (50,0)	13 (38,2)	11 (47,8)	-
Grade 2 (Detectable, but not lise-threatening cardiovascular reactions)	11 (14,7)	-	6 (17,6)	5 (21,7)	
Grade 3 (Shock, life-threatining smooth muscle spasms)	26 (34,7)	8 (44,4)	12 (35,3)	6 (26,1)	
Grade 4 (Cardiac arrest)	5 (6,7)	1 (5,6)	3 (8,8)	1 (4,3)	
Treatment of reactions; [n (%)]					
Short-acting antihistamine	1 (2,0)	-	1 (4,2)	-	-
Methylprednisolone	2 (4,1)	-	-	2 (15,4)	
Short-acting antihistamine+ Methylprednisolone	30 (61,2)	8 (66,7)	13 (54,2)	9 (69,2)	
Short-acting antihistamine+ Methylprednisolone + Adrenaline	16 (32,7)	4 (33,3)	10 (41,7)	2 (15,4)	
Culprit Drug; [n (%)]					-
Neuromuscular blocking agents (Rocuronium)	9 (12,0)	7 (38,9)	2 (5,9)	-	
Neuromuscular blocking agents (Vecuronium)	8 (10,7)	6 (33,3)	-	2 (8,7)	
Opioids (Fentanyl)	5 (6,7)	-	4 (11,8)	1 (4,3)	
Opioids (Aldolane)	4 (5,3)	1 (5,6)	-	3 (13,0)	
Opioids (Tramadol)	5 (6,7)	-	-	5 (21,7)	
Opioids (Morphine)	2 (2,7)	-	1 (2,9)	1 (4,3)	
Hypnotic (Mıdazolam)	7 (9,3)	1 (5,6)	5 (14,7)	1 (4,3)	
Hypnotic (Propofol)	6 (8,0)	-	6 (17,6)	-	
Antibiotic (Ampicillin Sulbactam)	1 (1,3)	-	-	1 (4,3)	
Antibiotic (Cefazolin)	6 (8,0)	3 (16,7)	3 (8,8)	-	
Antibiotic (Ciprofloxacin)	1 (1,3)	-	1 (2,9)	-	
Antibiotic (Ceftriaxone)	3 (4,0)	-	1 (2,9)	2 (8,7)	
H2 Receptor Antagonist (Ranitidine)	2 (2,7)	-	1 (2,9)	1 (4,3)	
Antiseptic (chlorhexidine)	6 (8,0)	-	6 (17,6)	-	
Latex	4 (5,3)	-	1 (2,9)	3 (13,0)	
NSAID (Paracetamol)	1 (1,3)	-	1 (2,9)	-	
NSAID (Dexketoprofen)	1 (1,3)	-	-	1 (4,3)	
Antibiotic (Cefazolin)+ Neuromuscular blocking agents (Rocuronium)	1 (1,3)	-	1 (2,9)	-	
Latex+ Hypnotic (Propofol)	1 (1,3)	-	-	1 (4,3)	
Latex+ Neuromuscular blocking agents (Rocuronium)	1 (1,3)	-	-	1 (4,3)	
Neuromuscular blocking agents (Rocuronium)+ Hypnotic (Propofol)	1 (1,3)	-	-	1 (4,3)	
Skin prick test positivity; [n (%)]	26 (35,1)	5 (27,8)	14 (41,2)	7 (31,8)	0,583**
Intradermal test positivity; [n (%)]	68 (98,6)	18 (100,0)	33 (100,0)	17 (94,4)	-
Cancellation of surgery; [n (%)]	30 (40,0)	8 (44,4)	20 (58,8)	2 (8,7)	**0,001****
Surgery after drug tests; [n (%)]	50 (66,7)	13 (72,2)	23 (67,6)	14 (60,9)	0,736**

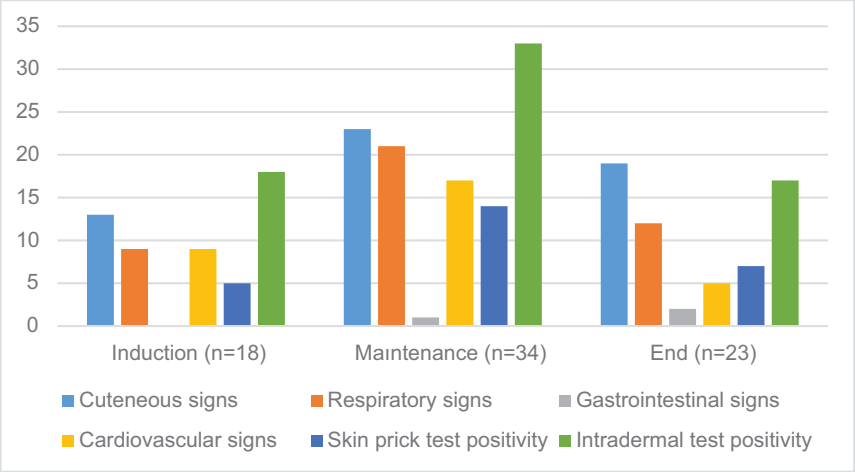

Figure 2 Distribution of system involvement; skin prick test and intradermal test positivity according to the time of POH.

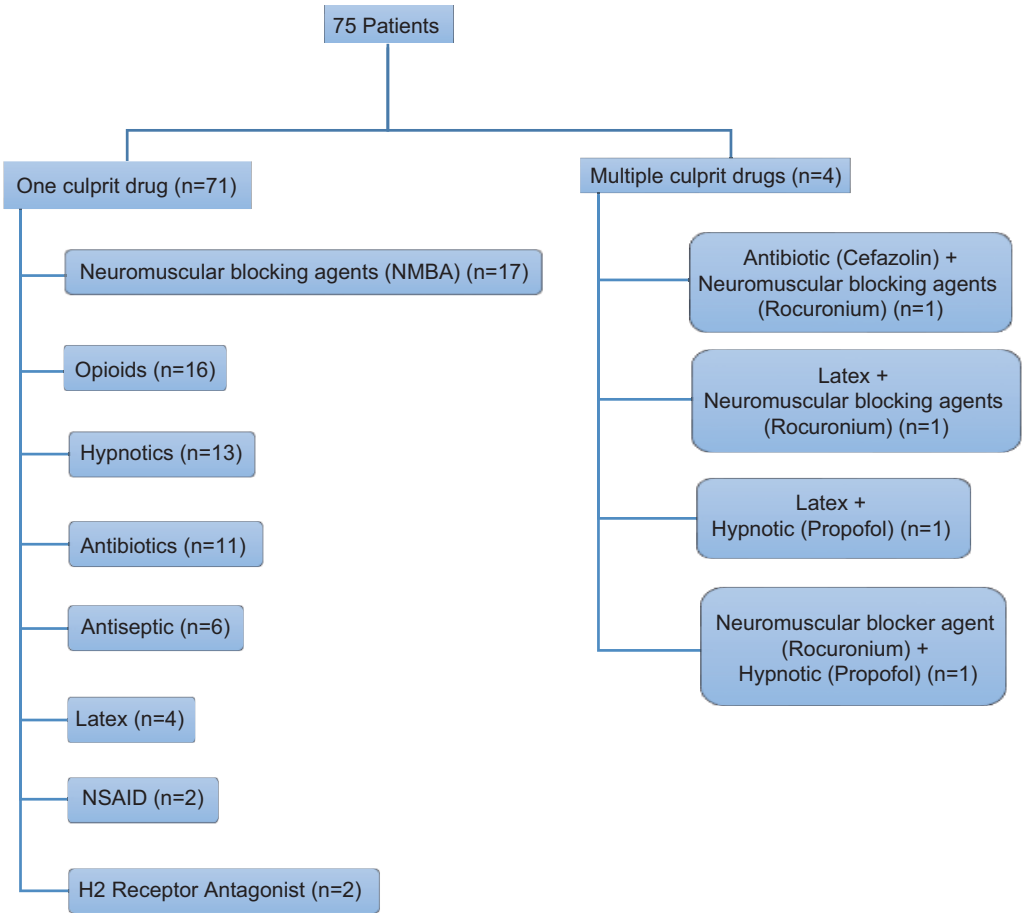

Figure 3 Distribution of culprit drugs from POH.

defined conditions cause the patient to seek unnecessary alternative medication. For this reason, intraoperative detailed notes can guide the subsequent processes more easily. Here too, anesthesia and allergist should be in cooperation.

In 75 patients, there were significantly more females than men with a female-to-male ratio of 8.3:1. In the study conducted by Annick et al. in Netherlands, it was significantly more common in females.[12] Atopy, asthma, presence of allergic diseases, and history of drug allergy were

Table 3 The study data of 75 patients due to POH.

Patient	Age	Gender	Brown	Ring Messmer	Timing	Symptoms	Operation Cancelled	Operatıon	Culprit Drug	Skin Prick Test	IDT	Operatıon after Culprit Drug Identıfıed
1	34	M	3	3	Maintenance	Cvs, Cu, Rsp	+	Ear-Nose-Throat surgery	Ranıtıdıne	-	+	+
2	49	F	1	1	Maintenance	Cu	-	Abdominal surgery	Rocuronium	-	+	+
3	62	F	2	2	Maintenance	Cvs, Cu, Rsp	+	Torax surgery /bronchoscopy	Cefazolin	+	+	+
4	68	M	2	2	Maintenance	Cu,Rsp	+	Orthopedic surgery	Chlorhexidine	-	+	+
5	25	F	2	2	End	Cu, Rsp	+	Ear-Nose-Throat surgery	Tramadol	-	+	+
6	58	F	3	3	End	Cvs,Rsp	-	Ear-Nose-Throat surgery	Fentanyl	-	+	+
7	37	F	1	1	Induction	Cu	-	Genitourinary system surgery	Rocuronium	-	+	+
8	53	F	2	2	End	Cu, Rsp	-	Genitourinary system surgery	Ampicillin Sulbactam	-	-****	+
9	44	F	1	1	Maintenance	Cu	-	Genitourinary system surgery	Chlorhexidine	-	+	+
10	61	F	2	2	Maintenance	Cu,Rsp	+	Dental treatment	Propofol	+	+	+
11	56	F	2	2	Maintenance	Rsp,Cvs	+	Orthopedic surgery	Fentanyl	+	+	+
12	25	F	1	1	Maintenance	Cu	+	Ear-Nose-Throat surgery	Mıdazolam	-	+	+
13	33	F	1	1	Maintenance	Cu	-	Dental treatment	Chlorhexidine	-	+	+
14	32	F	2	2	Maintenance	Cu,Rsp	+	Abdominal surgery	Propofol	+	+*	+
15	39	F	1	1	End	Cu	-	Genitourinary system surgery	Aldolane	-	+	+
16	33	F	3	3	End	Cu,Rsp	-	Cardiac surgery	Vecuronium	-	+	+
17	74	F	1	1	End	Cu	-	Breast surgery	Aldolane	+	+	+
18	50	F	1	1	Inductıon	Cu	+	Genitourinary system surgery	Cefazolin	-	+****	+
19	63	F	3**	4**	Maintenance	Rsp,Cvs	+	Genitourinary system surgery	Rocuronium	-	+	+
20	61	F	1	1	End	Cu	-	Orthopedic surgery	Latex # Porpofol	+ +	Ø +	-
21	33	F	1	1	Inductıon	Cu	-	Genitourinary system surgery	Vecuronium	-	+	+
22	23	F	3	3	Maintenance	Cu,Rsp,Cvs	-	Abdominal surgery	Paracetamol	-	+	-
23	25	F	3	3	End	Rsp,Cvs,Gis	-	Ear-Nose-Throat surgery	Dexketoprofen µ	+	Ø	+
24	65	F	3	3	Inductıon	Rsp,Cvs	+	Abdominal surgery	Rocuronium	-	+	+
25	50	F	1	1	Inductıon	Cu	-	Orthopedic surgery	Vecuronium	-	+	+
26	43	F	1	1	Maintenance	Cu	-	Genitourinary system surgery	Propofol	-	+	+
27	59	F	1	1	Inductıon	Cu	-	Endoscopy/ colonoscopy	Rocuronium	-	+	-
28	29	F	1	1	Maintenance	Cu	-	Ear-Nose-Throat surgery	Mıdazolam	-	+	-
29	53	F	3	3	Maintenance	Rsp, Cvs	+	Orthopedic surgery	Latex #	+	Ø	-
30	43	F	1	1	End	Cu	-	Genitourinary system surgery	Latex #	+	Ø	+
31	53	F	3**	4**	Maintenance	Rsp, Cvs	+	Abdominal surgery	Fentanyl	-	+	+

(*continues*)

Table 3 Continued.

Patient	Age	Gender	Brown	Ring Messmer	Timing	Symptoms	Operation Cancelled	Operation	Culprit Drug	Skin Prick Test	IDT	Operation after Culprit Drug Identified
32	43	F	3	3	Induction	Rsp, Cvs	+	Genitourinary system surgery	Vecuronium	-	+	+
33	46	F	1	1	Maintenance	Cu	-	Endoscopy/ colonoscopy	Midazolam	-	+	+
34	59	F	3	3	End	Cu, Rsp	+	Genitourinary system surgery	Ceftriaxone	Ø***	Ø***	+
35	68	F	3	3	Maintenance	Rsp, Cvs	+	Abdominal surgery	Midazolam	+	+	-
36	60	F	3	3	Induction	Rsp, Cvs	+	Breast surgery	Vecuronium	-	+	+
37	31	F	2	2	End	Rsp, Cu	-	Genitourinary system surgery	Tramadol	-	+	-
38	69	F	1	1	Maintenance	Cu	-	Orthopedic surgery	Cefazolin	-	+	+
39	31	M	3	3	Induction	Cu, Cvs, Rsp	+	Ear-Nose-Throat surgery	Cefazolin ***	-	+	-
									Rokuronyum	-	+	
40	57	F	3	3	Maintenance	Cvs, Rsp, Gis	+	Genitourinary system surgery	Ceftriaxone	-	+	-
41	30	F	3	3	Maintenance	Cu, Cvs, Rsp	+	Genitourinary system surgery	Ciprofloxacin	+	+	+
42	44	F	1	1	End	Cu	-	Ear-Nose-Throat surgery	Latex #	+	Ø	+
43	29	M	2	2	End	Cu, Rsp	-	Genitourinary system surgery	Tramadol	-	+	-
44	50	F	1	1	Induction	Cu	-	Genitourinary system surgery	Rokuronyum	-	+	-
45	42	M	1	1	End	Cu	-	Orthopedic surgery	Aldolane	-	+	-
46	72	F	3**	4**	Induction	Cu, Rsp, Cvs	+	Ear-Nose-Throat surgery	Vecuronium	-	+	-
47	51	F	1	1	End	Cu	-	Endoscopy/ colonoscopy	Midazolam	-	+	+
48	45	F	1	1	Maintenance	Cu	-	Genitourinary system surgery	Propofol	+	+	+
49	54	F	1	1	End	Cu	-	Abdominal surgery	Morphine	-	+	-
50	59	F	3	3	Maintenance	Cvs, Rsp	+	Abdominal surgery	Fentanyl	-	+	-
51	55	F	1	1	End	Cu	-	Abdominal surgery	Vecuronium	-	+	-
52	41	F	1	1	Induction	Cu	-	Ear-Nose-Throat surgery	Cefazolin	-	+	-
53	55	F	1	1	End	Cu	-	Genitourinary system surgery	Ranitidine	-	+	-
54	53	M	1	1	Maintenance	Cu	-	Endoscopy/ colonoscopy	Rocuronium	-	+	-
									Latex #	+	Ø	
55	47	F	3	3	Induction	Cu, Rsp, Cvs	+	Genitourinary system surgery	Aldolane	+	+	+
56	64	F	3	3	Induction	Cu, Rsp, Cvs	+	Abdominal surgery	Rocuronium	-	+	+
57	23	F	2	3	End	Cu, Rsp	-	Genitourinary system surgery	Tramadol	-	+	-
58	80	F	3	3	Maintenance	Rsp, Cvs	+	Genitourinary system surgery	Fentanyl	+	+	-
59	39	F	1	1	Maintenance	Cu	-	Orthopedic surgery	Midazolam	-	-	-
60	45	F	1	1	End	Cu	-	Orthopedic surgery	Latex #	+	Ø	+
61	33	M	3	3	Maintenance	Rsp, Cvs	-	Orthopedic surgery	Cefazolin	-	+	-
62	30	M	3	3	End	Rsp, Cvs	-	Ear-Nose-Throat surgery	Rocuronium	-	+	-
									Propofol	-	+	
63	24	F	3	3	Induction	Rsp, Cvs	-	Ear-Nose-Throat surgery	Rocuronium	+	+	+
64	53	F	3	4**	End	Cu, Cvs, Gis	-	Abdominal surgery	Ceftriaxone	+	+	+
65	40	F	3	4**	Maintenance	Cvs, Rsp	+	Genitourinary system surgery	Chlorhexidine	-	+	+

66	50	F	2	2	End	Cvs, Rsp	-	Abdominal surgery	Tramadol	-	+	+
67	63	F	2	3	Induction	Cvs, Rsp	-	Orthopedic surgery	Vecuronium	-	+	+
68	48	F	1	1	Maintenance	Cu	-	Genitourinary system surgery	Chlorhexidine	+	+	+
69	31	F	1	1	Maintenance	Cu	-	Dental treatment	Chlorhexidine	+	+	+
70	70	F	3	3	Maintenance	Cvs, Rsp	+	Genitourinary system surgery	Propofol	-	+	+
71	62	F	1	1	Induction	Cu	-	Abdominal surgery	Rocuronium	-	+	+
72	34	F	1	1	İnduction	Cu	-	Ear-Nose-Throat surgery	Cefazolin	+	+	+
73	33	F	3	3	İnduction	Cu, Rsp, Cvs	+	Torax surgery /bronchoscopy	Midazolam	+	+	-
74	49	F	1	1	Maintenance	Cu	-	Abdominal surgery	Propofol	+	+	+
75	37	F	3	3	Maintenance	Cu, Rsp, Cvs	+	Genitourinary system surgery	Morphine	+	+	+

M: Male; F: Female; RM: Ring Mesmmer grading score; Cvs: cardiovascular signs; Cu: cutaneous signs; Rsp: Respiratory signs; Gis: gastrointestinal signs; Timing: End; Induction; Maintenance: Induction: Ten minutes after the start of the anesthesia.
End: End of the surgery. Maintenance: Between induction and end of anesthesia.
(*egg white and yolk prick test positive; **cardiopulmonary resuscitation; ***basophil activation test is positive; ****Drug provacation test positive; #Spesifik Ige Positive ; µ enhanced reaction to the same drug for the second time; Ø Not done.)

not found to be risk factors for POH. Similar to our study, in a meta-analysis, including 19 studies, the presence of atopy and drug allergy were not found to be risk factors in immune-mediated perioperative anaphylaxis.[13]

Cutaneous, cardiovascular, and respiratory systems were most frequently affected in our study (73.3%; 56%; 41.3%). The most frequently affected systems were found to be the same in studies conducted in Belgium.[14,15] While the number of patients who developed both Brown grade 2-3 and Ring and Messmer grade 2-3-4 reactions, that is, perioperative anaphylaxis, was 45, the number of patients who received adrenaline was 16. In the JESPA (Japanese Epidemiologic Study for Perioperative Anaphylaxis) study conducted in Japan on adrenaline awareness in perioperative anaphylaxis, it is noteworthy that adrenaline was administered to 30 of 43 patients who were evaluated as definite perioperative anaphylaxis.[16] In a Chinese study, adrenaline was administered to 51.9% of patients, even in patients with near-fatal and fatal perioperative anaphylaxis.[17] This shows that physicians still need to be aware that adrenaline is the first line treatment for anaphylaxis.

Diagnostic tests with drugs used in POH anesthesia are recommended.[18] NMBAs were the greatest number of culprit agents responsible for POH in our study similar to data from France and Australia,[19] whereas antibiotics were the most common culprit agents in studies conducted in the USA and Netherlands.[20,10]

In NMBA, POH was observed with rocuronium in 12 patients, with vecuronium in 8 patients. Similar data were found in the literature. In an Australian study, perioperative anaphylaxis was more common with rocuronium than with vecuronium.[21] In the 11th GERAP (Groupe d'Etude des Réactions Anaphylactiques Périopératoires) survey study in France, rocuronium was considered riskier.[22] As a result of epidemiological studies, according to the NAP6 (6th National Audit Project) study, anesthetists thought that rocuronium was more POH and avoided this drug.[23]

POH with antibiotics has been reported especially with cephalosporins among betalactam antibiotics.[18] Similarly, in our study, the culprit drug of POH in 11 patients was antibiotics, 10 of them were betalactam antibiotics.

Chlorhexidine is a synthetic biguanide with antibacterial activity and a potential culprit in POH. Information about chlorhexidine and POH is increasing day by day in the literature. Reactions with chlorhexidine developed in six patients, anaphylaxis developed in two, and isolated cutaneous system was affected in four. Similarly, in a study in China in which 10 patients with isolated chlorhexidine allergy were examined individually, it was emphasized that POH reactions could be of any severity.[24]

Skin prick test and IDT are the main diagnostic tests to identify the culprit drug in POH.[14]

Patients with a history of anaphylaxis with NMBA were evaluated for reexposure to NMBA after skin tests were negative; while 80% (12/15) completed the procedure safely, 20% (3/15) developed hypotension.[25] In our study, all patients (50/75) who received reanesthesia were able to complete the operation successfully. The index reaction in the patients in the study was not only anaphylaxis but also isolated skin involvement. Therefore, the rate of development of hypersensitivity in cases of reanesthesia may have been lower in our study compared to the literature.

In our study, opioids were the second most common drug group responsible for POH, after NMBA. They are one of the most common drug allergy labels and important for patients with acute and chronic pain. Therefore, skin prick tests and specific IgE measurement are recommended if opioids are among the drugs suspected of POH. Skin prick test is still the gold standard.[26] In our study, the diagnosis was made by the skin prick test.

Propofol-induced POH was seen in eight patients, where one had urticaria after eating egg. Skin prick test with egg yolk, egg white, and soya was positive. Anaphylaxis developed when propofol was administered for abdominal surgery. Moreover, urticaria persisted for months. Skin prick tests with egg yolk and egg white were negative in the remaining seven patients. Propofol contains refined soya bean oil and egg lecithin. There is no conclusive evidence of contraindication to the use of propofol in patients allergic to egg, soya, or peanut[27,4]; however, if the patient has a history of hypersensitivity to egg, soya, or peanut before anesthesia, skin prick test, or specific IgE positivity, we conclude that skin tests are important for propofol.

Hypersensitivity reactions to latex have been caused by the increased use of latex, especially with the human immunodeficiency virus epidemic.[28] With this realization, better quality latex and powder-free gloves were used. In this case, it is mentioned that hypersensitivity decreased.[29] However, the use of latex products also increased in the SARS-CoV-2 outbreak; therefore, there may have been a change in the process. In our patient group, hypersensitivity to latex was observed in six patients (isolated skin involvement in five patients and anaphylaxis in one patient).

In our study, the operation was continued in 60% of the patients after POH developed. We looked at the severity of POH/number of patients whose operation was cancelled/number of patients whose operation was continued; grade 1 (33)/2/31, grade 2 (13)/7/6, grade 3 (29)/21/8. In patients with grade 2 and grade 3 POH, the physicians decided to cancel the operation more often; in grade 1 POH, they decided to continue the operation more often. If the patient is stabilized after POH, it is recommended to continue the operation to avoid reanesthesia.[27] Moreover, it was observed that there was no extra risk in patients who continued the operation after POH compared to patients in whom the operation was cancelled.[30]

The most important limitation of our study is that our hospital is a tertiary referral hospital. Generally, patients from all over the country are admitted, but severe POH patients are more frequently referred. Therefore, the study population may not reflect all POH adult patients. In addition, patient files were analyzed retrospectively. The strengths of our study are that a large number of patients were evaluated due to our being a reference hospital. As a result, while the drug group we found to be responsible for POH most frequently was NMBA, reanesthesia situations are safe after allergist evaluation.

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Authors' Consent for Publication

All authors approve this manuscript to be submitted to a journal.

Availability of Data and Materials

The data that support the findings of this study are not publicly available due their containing information that could compromise the privacy of research participants but are available from ZYK, IB.

Ethics Approval and Consent to Participate

Ethics committee approval of the University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital was obtained for this study.

Authors Contributions

All authors take part of Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

Conflicts of Interest

The authors declare no conflicts of interest.

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