

The usefulness of plasma histamine and different tryptase cut-off points in the diagnosis of peranaesthetic hypersensitivity reactions

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Summary

Anaesthetic hypersensitivity reactions can be IgE- or not IgE-mediated and are a challenge to find the causal agent. Histamine and tryptase determination are classically considered useful in the diagnosis of these reactions. The aim of our study was to assess the diagnostic usefulness of plasma histamine and different cut-off points of serum tryptase. **Methods** Patients suffering a reaction suggestive of hypersensitivity during general anaesthesia in Clínica Universidad de Navarra (2008–2012) were included. Serum tryptase and plasma histamine were measured at the time of the reaction and 2 h later. Baseline tryptase was also determined. Four to eight weeks after the reaction an allergological study was performed to all the drugs or products involved in the reaction.

Results Sixty-five patients suffered an immediate hypersensitivity reaction during the period of the study. Thirty-seven patients (20 male) with median age 48 years (12–79) were included because they completed allergological study, and histamine and tryptase were correctly obtained. Elevated plasma histamine was observed in 34 cases (92%). Tryptase exceeded twice the basal values in 10 patients (31%). Using different cut-off points of tryptase, the number of patients with elevated tryptase would be 15 patients (41%) for a cut-off point of 5 µg/L; 12 patients (32%) for a cut-off point of 8.23 µg/L; nine patients (24%) for 10.5 µg/L; and eight patients (22%) for 11.4 µg/L. The median tryptase level for the IgE-mediated reactions was 9.0 µg/L (2–70 µg/L) and 4.0 µg/L (3–13 µg/L) in non-IgE-mediated reactions ($P < 0.01$). Median tryptase levels were higher in more severe reactions (grade 2 or 3) in comparison with grade 1. The best ratio for serum-tryptase-during-reaction/basal-serum-tryptase to discriminate between IgE and non-IgE reactions was 2.0.

Conclusion The best criterion for discriminating IgE- and non IgE-mediated hypersensitivity reactions in anaesthesia was a tryptase value exceeding twice the basal one.

Keywords anaphylaxis, anaesthesia, histamine, hypersensitivity, tryptase

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Introduction

Perioperative adverse reactions secondary to the administration of anaesthetic agents or other drugs administered during the induction of anaesthesia or during the course of the procedure have been the focus of many studies. The intensity of these reactions is very variable and may put the life of the patient at risk. They may

occur at any moment during the operation although approximately half occur during the induction phase [1].

The mechanism of these reactions may or may not be IgE-mediated. Allergological study should be performed 4–6 weeks after the reaction occurred. However, recently, a high percentage of positive results have been demonstrated when skin tests had been performed during the first 4 days after the reaction [2]. When IgE is not detected, other possible mechanisms exist such as the non-specific release of histamine, complement

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activation or the mediation of other antibodies [3, 4]. At the moment of the reaction, doubts may exist as to whether a hypersensitivity reaction is taking place or another diagnosis may be posited (for example, mechanical involvement of the airways, myocardial ischaemia or others).

To confirm the allergic nature of the reaction serum tryptase and plasma histamine levels during the reaction can be measured. High levels of these mediators suggest a hypersensitivity reaction. Furthermore, histamine and tryptase levels together with the results from skin tests with the drugs involved may help diagnose if the reaction is IgE-mediated or not and identify the causal agent. According to past studies, more than half of the cases are reactions mediated by IgE [1, 5].

Tryptase is a serum protease present in mast cells and basophils. The tryptase content in basophils is approximately 1% of the tryptase content in mast cells and thus elevated serum tryptase levels in a reaction can be understood as indicating mast cell activation [6]. Tryptase determination for the diagnosis of anaphylaxis has a low sensitivity with a positive predictive value of 92.6% and a negative predictive value of only 54.3% [7]. Tryptase is released from the mast cells in a protease–proteoglycan complex which diffuses slowly peaking between 15 and 120 min after its release. In the literature, no consensus exists over what should be the cut-off point for considering tryptase levels to be high for a hypersensitivity reaction, and different figures have been used in different studies [8, 9]. Current recommendations from the Thermo Fisher laboratory establish the limit of serum tryptase at 11.4 µg/L using the ImmunoCAP technique as this represented the 95th percentile of the 129 control subjects included in their study. Enrique et al. [8] established the cut-off point for serum tryptase at 8.23 µg/L with a sensitivity of 94.12% and a specificity of 93.2%.

Histamine is vasoactive hydrophilic amine product of the decarboxylation of the histidine amino acid. Once histamine is formed, it is rapidly stored or inactivated. The role of histamine in immediate hypersensitivity reactions is well known where it acts as the most important mediator which produces the majority of signs and symptoms in these reactions. During a hypersensitivity reaction, histamine is released from the mast cells and basophils in parallel with tryptase. However, unlike tryptase, histamine is not associated with any protein complex and thus reaches its peak 5–15 min after the onset of the reaction and then decreases to baseline levels after 30 min [10]. Some studies suggest that levels of plasma histamine are correlated with the severity of the reaction [11].

The aim of our study was to compare the diagnostic yield of the determination of plasma histamine and serum tryptase during the reaction in patients suffering

an adverse reaction suggestive of immediate hypersensitivity during general anaesthesia.

Materials and methods

Patients

We carried out a prospective study between March 2008 and April 2012 in which all patients who suffered a perioperative hypersensitivity reaction at any time during induction, maintenance or post-surgical recovery in generalized anaesthesia were included. The next were considered as symptoms from a perioperative hypersensitivity reaction: erythema, weals, pruritus, angio-oedema, bronchospasm, increased airway pressure, desaturation < 90%, wheezing, hypo/hypertension, dysrhythmia, ST changes, bradycardia/tachycardia, nasoconjunctival symptoms, hypo/hyperthermia, convulsion, abdominal symptoms and cardiac arrest. Patients whose only manifestation was hypotension or bronchospasm were included if there was no other cause to justify such symptoms. When the only symptom was generalized erythema, only those patients in whom the exanthema lasted for more than three minutes were included.

Serum tryptase and plasma histamine were determined at the time of the reaction (0–15 min from onset) and again at 2 h. Furthermore, baseline tryptase levels were also measured 24 or more hours after the reaction. Those patients in whom histamine and tryptase were not extracted at the same time and those patients that did not complete allergological study were excluded from the analysis. The severity of the reaction was established following the classification of Ring and Messmer [12] as grade 1, grade 2, grade 3 and grade 4. Reactions were classified as IgE-mediated or not according to the result of skin tests performed, that are described below. The study was approved by the ethics committee, and all the participants were informed about the protocol and provided written informed consent.

Plasma histamine

The heparinized blood was processed immediately and/or kept at 4°C (a maximum of 24–48 h) after its extraction and subsequently centrifuged to separate the plasma that was processed afterwards to quantify the amount of histamine.

Plasma histamine was determined using the fluorometric method following the technique described by Shore and modified by Siraganian [13, 14] with an AutoAnalyzer 3 (Bran Luebbe, SEAL Analytical Inc, Mequon, WI, USA). Plasma histamine was also determined as controls to 37 patients undergoing general anaesthesia with administration of a muscle relaxant

(atracurium besylate, cisatracurium or rocuronium), not presenting a hypersensitivity reaction, in a sample obtained 5–15 min after induction of the anaesthesia, to determine whether the drugs administered during induction were capable of producing a non-specific increase in histamine levels. The cut-off point for elevated histamine established in our laboratory is 28 ng/mL, having a sensitivity of 74.51 and a specificity of 80.7%.

Tryptase determination

Tryptase was determined using an enzyme immunoassay (ImmunoCAP FEIA, Thermo Fisher, Uppsala, Sweden) [9].

Cut-off points

To determine the utility of tryptase determination to differentiate IgE-mediated reactions of those non-IgE-mediated, cut-offs were established by receiver operating characteristics curve (ROC curve) according to the best sensitivity and specificity values calculated. ROC curves were calculated using MedCalc software (v. 12.7.2; Ostend, Belgium).

The next cut-offs of serum tryptase reported in the literature were selected to assess the value of those cut-offs in discriminating IgE- and non-IgE-mediated reactions: 11.4 µg/L, recommended by Thermo Fisher for its ImmunoCAP technique (it was the 95th percentile of 129 control subjects); 8.23 µg/L, the cut-off reported by Enrique *et al.* [8], with a sensitivity of 94.12% and specificity 92.31%; and 10.5 µg/L, used by Schwartz [9] as it represented the mean tryptase level plus 2 standard deviations in the control subjects.

Allergological study

Prick and intradermal skin tests were performed two times: during the first 4 days after the reaction (data not analysed in the study), and between 4 and 8 weeks after the reaction. All the drugs administered to the patient up until the reaction occurred were tested. The allergological study was considered positive if a skin test resulted positive at early or late study.

For each drug, we used the dilution recommended by guidelines [15]. For those drugs for which no reference dilutions were available, 10 controls were performed to guarantee that the dilutions used did not produce irritation.

Statistical analysis

Quantitative variables were described as median (Range) and were compared by using Mann–Whitney U-test. All

data were analysed using the software package SPSS v.15.0 (Chicago, IL, USA). Normality was assessed by Shapiro–Wilk test. All *P*-values < 0.05 were considered statistically significant.

Results

During the time period (2008–2012), 65 patients who had suffered a perioperative reaction were referred to our department. Thirty-seven patients completed the allergy study and were included. Of the 37 patients included, twenty were male and 17 were female. Their median age was 48 years (12–79). Twelve (32%) of patients had a history of atopy. Table 1 shows the patient data.

Seventeen (46%) of the reactions occurred during the induction of anaesthesia, 13 (35%) during the operation, seven (19%) in Post-Anesthesia Care Unit (PACU).

With regard to severity, 21 reactions (57%) were classed as grade 1, seven (19%) as grade 2 and 9 (24%) as grade 3. There were no cases of grade 4 reactions.

The most common sign was generalized erythema, which affected 24 patients (65%) followed by hypotension (nine cases; 24%) and increased airway pressure (seven cases; 19%). Seven patients presented cardiac abnormalities (two arrhythmia, one ST change and three changes in heart rate). Four (11%) patients presented a fall in saturation below 90%. Five (13%) patients who were conscious at the onset of the reaction reported pruritus.

The allergological study showed in 19 patients an IgE-mediated mechanism against one of the drugs administered or products used. All of them were diagnosed by skin tests. The drugs most commonly involved were muscle relaxants in seven patients, antibiotics in six patients, latex in two patients and four had a reaction to another drug (plasma expanders, metamizol, protamine and povidone iodine). It is worth noting that of the 21 patients with grade 1 reaction that completed the allergological study, in nine (43%), the reaction had been mediated by IgE. Of the 16 patients with grade 2 or grade 3 reactions, 10 (63%) were IgE-mediated.

Plasma histamine values

Elevated plasma histamine (> 28 ng/mL) was observed in 34 cases (92%) who experienced a reaction to the anaesthesia.

The median plasma histamine of all the cases at the beginning of the reaction was 35 ng/mL (15–143) and at 2 h 34 ng/mL (14–133). These differences were not statistically significant (*P* = 0.165). Median plasma histamine for controls was 23.4 ng/mL (6.2–36.5). Differences between plasma histamine from controls and

Table 1. Summary of patient data

No	Sex	Age	Time of reaction	Drug causing the reaction mediated by IgE	Tryptase* (µg/L)	Tryptase† (µg/L)	Baseline tryptase (µg/L)	Tryptase doubling	Histamine* (ng/mL)	Histamine† 2 h (ng/mL)	Severity of the reaction
1	F	52	PACU	NA	1.95	2.05	3.05	No	38.51	26.54	1
2	M	55	Operation	Amoxicillin	6.69	8.99	3.43	Yes	14.79	46.72	3
3	M	48	PACU	NA	6.46	5.44	NR	ND	19.29	14.32	1
4	M	58	Induction	NA	4.67	NR	NR	ND	60.85	NR	1
5	F	12	PACU	NA	2.98	2.00	NR	ND	17.31	15.14	1
6	F	33	PACU	Gelafundin®	1.85	2.07	1.65	No	26.89	29.57	1
7	F	79	Operation	Latex	47.50	69.50	11.60	Yes	45.79	19.83	2
8	M	17	Operation	Latex	6.35	28.30	6.17	Yes	32.14	18.73	1
9	F	49	PACU	Amoxicillin	3.27	5.94	2.65	Yes	33.41	29.11	1
10	M	23	Induction	Atracurium	23.60	17.80	1.66	Yes	69.98	25.02	3
11	F	37	Operation	Gelafundin®	9.18	4.79	2.53	Yes	29.30	34.38	2
12	F	46	Induction	NA	3.51	3.47	4.39	No	33.21	NR	3
13	M	61	Induction	NA	12.00	11.30	10.50	No	37.01	28.53	3
14	F	56	Operation	dipyrene	33.90	46.00	5.71	Yes	36.72	NR	2
15	F	19	Operation	NA	7.21	5.72	6.19	No	48.33	45.79	1
16	F	34	Operation	NA	3.24	2.05	1.74	No	34.93	35.95	2
17	M	67	PACU	NA	6.74	6.45	5.74	No	36.94	26.58	1
18	M	25	PACU	NA	2.32	2.55	2.99	No	28.42	NR	1
19	F	32	Induction	NA	6.10	5.64	3.94	No	49.46	39.41	3
29	M	72	Induction	NA	8.21	7.94	7.81	No	143.4	132.72	1
21	M	64	Operation	Amoxicillin–clavulanic acid	9.60	11.30	3.12	Yes	40.91	36.44	2
22	F	48	Induction	NA	3.07	1.83	2.89	No	29.97	NR	1
23	M	20	Induction	Atracurium	3.28	3.01	2.73	No	45.72	49.01	3
24	M	64	Induction	Amoxicillin–clavulanic acid	34.70	28.90	5.45	Yes	74.35	NR	3
25	F	62	Induction	Atracurium	6.99	5.53	4.18	No	38.87	37.32	1
26	M	15	Induction	Atracurium	13.80	12.30	3.23	Yes	36.54	36.54	3
27	M	12	Induction	NA	3.12	2.06	1.71	No	81.29	85.39	1
28	M	75	Induction	NA	2.97	3.47	3.49	No	33.44	41.84	1
29	F	57	Operation	NA	7.09	7.05	7.01	No	28.28	26.94	2
30	M	24	Induction	Atracurium	8.30	7.39	6.52	No	28.49	30.19	1
31	M	64	Operation	Levofloxacin	6.12	6.17	NR	ND	31.70	24.07	1
32	F	16	Operation	NA	5.06	4.02	4.90	No	27.79	27.47	3
33	M	54	Operation	Protamine	11.60	18.60	19.00	No	33.33	47.33	2
34	F	51	Induction	Povidone	3.30	3.17	NR	ND	32.21	26.90	1
35	M	15	Induction	Atracurium	4.46	4.89	4.87	No	18.75	36.11	1
36	M	19	Induction	NA	2.62	2.40	2.81	No	41.55	43.82	1
37	F	53	Operation	Cefazolin	5.49	3.12	3.08	No	66.90	65.18	1

*First blood extraction at 0–15 min from beginning of reaction.

†Second blood extraction at 2 h from beginning of reaction.

M, male; F, female; NA, not IgE-mediated; NR, not realized; ND, not determined; PACU, Post-Anesthesia Care Unit.

Severity of the reaction: according to the classification of Ring and Messmer.

both determination in cases were statistically significant ($P < 0.001$).

Plasma histamine was increased in 100% of the patients with an IgE-mediated reaction and in 83% of non-IgE-mediated reactions.

The differences in the median of the histamine in IgE-mediated reactions (39 ng/mL; 30–74 ng/mL) and in non-IgE-mediated reactions (36 ng/mL; 17–143 ng/mL) were not statistically different (Fig. 1). No differences were found between the median of the his-

tamine neither depending on the drug group causing the reaction nor the severity of reaction (Table 2). There were no differences in the concentration of plasma histamine between atopic and non-atopic patients.

Serum tryptase values

Differences in the number of IgE-mediated or non-IgE-mediated reactions according to different cut-off points of tryptase were studied.

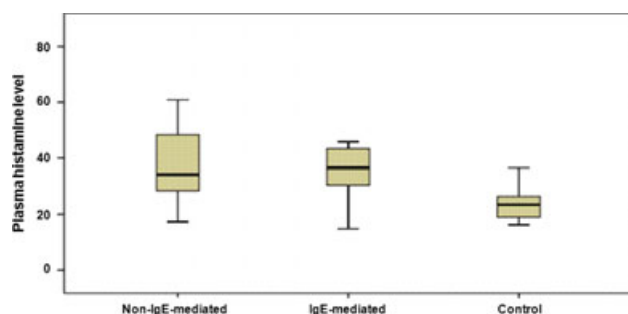


Fig. 1. Plasma histamine levels (ng/mL) in non-IgE-mediated reactions, IgE-mediated reactions and controls. Differences found between IgE-mediated and controls, and between non-IgE-mediated reactions and controls were statistically different ($P < 0.001$).

Table 2. Medians and interquartile range (IQR) of plasma histamine and tryptase levels depending on severity of reaction, the mechanism involved and the medication group causing the reaction

	Levels of plasma histamine and tryptase	
	Plasma histamine median ng/mL (Range)	Tryptase median $\mu\text{g/L}$ (Range)
Severity of the reaction		
Grade 1 ($n = 21$)	36 (17–143)	5 (2–28)*
Grade 2 ($n = 7$)	37 (28–47)	11 (3–70)*
Grade 3 ($n = 9$)	47 (28–74)	9 (3–35)*
Mechanism		
IgE-mediated ($n = 19$)	39 (30–74)	9 (2–70)†
Non-IgE-mediated ($n = 18$)	36 (17–143)	4 (3–13)
Drug group		
ATB ($n = 6$)	44 (32–74)	8 (5–35)
Anaesthetics ($n = 7$)	39 (30–70)	7 (2–24)
Latex ($n = 2$)	39 (32–46)	49 (28–70)
Others ($n = 4$)	35 (30–47)	14 (2–46)

*Difference between grade 1 and 2 reactions: $P < 0.01$; and between grade 1 and 3: $P < 0.05$.

†Difference between IgE-mediated and non-IgE-mediated reactions: $P < 0.01$.

Median baseline tryptase was 4 $\mu\text{g/L}$ (2–19), being significantly lower than tryptase value at beginning of the reaction [6 $\mu\text{g/L}$ (2–48); $P < 0.001$] and tryptase value at 2 h [6 $\mu\text{g/L}$ (2–70); $P < 0.01$], whereas the differences of tryptase value from the reaction and at 2 h were not statistically significant ($P = 0.275$).

Median serum tryptase value in the reaction in atopic patients was 9 $\mu\text{g/L}$ (3–46), and was significantly higher compared with non-atopic patients (5 $\mu\text{g/L}$; range 2–69) ($P < 0.05$). According to the severity of the reaction, median tryptase levels were significantly lower in grade 1 reactions compared with grade 2 ($P < 0.01$) and compared with grade 3 ($P < 0.05$). The difference in serum

tryptase levels between grade 2 and grade 3 was not statistically significant ($P = 0.427$).

No significant differences were seen in median tryptase levels depending on the drug group responsible for the reaction (Table 2).

The median tryptase level for the IgE-mediated reactions was 9 $\mu\text{g/L}$ (2–70) and 4 $\mu\text{g/L}$ (3–13) in non-IgE-mediated reactions ($P < 0.01$).

A ROC curve was performed to obtain the best cut-off point for serum tryptase to discriminate between IgE- or non-IgE-mediated reactions in our population. The best cut-off was 5 $\mu\text{g/L}$, with a sensitivity of 78.9% (CI 54.4–93.8%) and specificity 61.1% (CI 35.8–82.6%). Other cut-off points for serum tryptase used in bibliography had the next values: for 11.4 $\mu\text{g/L}$ established by Thermo Fisher laboratory, the sensitivity was 36.84% (CI 16.4–61.6%) and specificity 94.44% (CI 72.6–99.1%); for 10.5 $\mu\text{g/L}$ [10] the assay sensitivity was 42.1% (CI 20.3–66.5%) and specificity of 94.4% (CI 72.6–99.1%); for 8.23 $\mu\text{g/L}$ [8] the assay sensitivity was 57.9% (CI 33.5–79.7%) and specificity of 94.4% (CI 72.6–99.1%).

The ratio [serum tryptase during reaction/baseline serum tryptase] was 2.4 (0.7–14) in IgE-mediated reactions and 1.17 (0.8–1.9) in non-IgE-mediated reactions. A ROC curve was performed to obtain the best value of this ratio for serum tryptase to discriminate between IgE- or non-IgE-mediated reactions in our population (Fig. 2). The best ratio was 2.0, with a sensitivity of 55.6% (CI 30.8–78.4%) and specificity of 100% (CI 76.7–100%). This result did not improve when combined criteria (twofold rise of basal tryptase value plus a cut-off point for peak tryptase) were used, for any of the cut-off points.

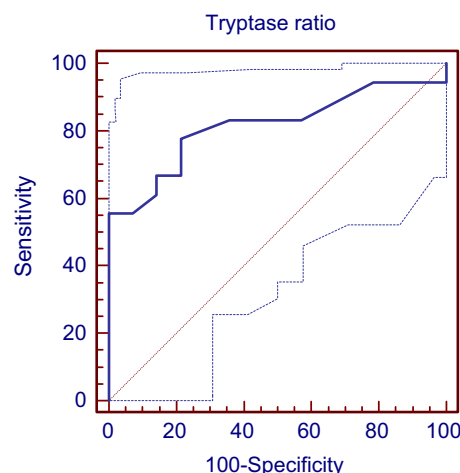


Fig. 2. ROC curve to obtain the best value of ratio between serum tryptase during reaction and baseline serum tryptase to discriminate IgE- or non-IgE-mediated reactions. Bold line represents ROC curve. Dashed lines represent 95% confidence intervals of the ROC curve.

Using different cut-off points of tryptase in the reaction, the number of patients with elevated tryptase would be the following: 15 (41%) patients for a cut-off of 5 µg/L; 12 patients (32%) for a cut-off point of 8.23 µg/L; nine patients (24%) for 10.5 µg/L; and eight patients (22) for 11.4 µg/L.

The number of patients diagnosed as having an IgE-mediated reaction using each of the cut-off points gave above is described in Table 3. All the patients whose tryptase value during the reaction exceeded twice basal one (10 patients, 27%) had an IgE-mediated reaction. One of these (Table 1, N 9) would only have met the criterion of elevated tryptase using the 5.0 µg/L cut-off point. Eight of those 10 patients (80%) experienced grade 2 and 3 reactions (Table 1).

However, using as the cut-off point serum tryptase greater than 5 µg/L, eight patients with non-IgE-mediated reactions are detected. With cut-off points 8.23 µg/L, 10.5 µg/L or 11.4 µg/L, one patient (Table 1, N 13) with elevated tryptase had a reaction that was not IgE-mediated. Furthermore, two patients who suffered an IgE-mediated reaction (Table 1, N 30 and 33) had high tryptase levels using the cut-off point of > 8.23 µg/L but did not exceed twice the basal one. Finally, two patients (Table 1, N 6 and 23) who suffered an IgE-mediated reaction did not show elevated tryptase using any of the parameters.

Discussion

In some reactions that occur during surgical operations, especially in those in which the signs and symptoms are mainly cardiovascular, an immediate hypersensitivity reaction may not be suspected [16, 17]. For this reason, the determination of serum tryptase and plasma histamine is useful as complementary measures for the diagnosis of a perioperative adverse reaction as they allow the participation of mast cells and/or basophils in the reaction to be confirmed and provide an orientation as to the probable mechanism involved.

Results of histamine determination in our patients differ from those obtained using a different method as radioimmunoassay. Nevertheless, they are similar to those obtained by other authors who used our same method [18]. Also, histamine values measured 2 h after the reaction did not show a fast reduction, compared with first determination, as should be expected. We cannot explain this result, although we cannot discard a persistent histamine release.

It is worth highlighting how in our series histamine was elevated in the majority of the patients (92%) unlike tryptase, which was only raised in 31% of cases when the criterion for elevation was exceeding twice basal values of tryptase. This greater sensitivity of histamine as compared to tryptase has long been known [19] and is consistent with results obtained in a study carried out in patients visiting emergency departments due to a hypersensitivity reaction [20]. Therefore, when considering if specific symptoms appearing during anaesthesia correspond to a possible hypersensitivity reaction, the determination of plasma histamine is very useful and offers a high sensitivity. Further studies are needed to analyse specificity.

However, histamine levels in blood do not allow IgE-mediated reactions to be distinguished from non-IgE-mediated reactions. In this regard, tryptase is much more specific with a clear relationship between elevated tryptase and IgE-mediated reactions. [21, 22]. According to our results, 27% of patients suffering a hypersensitivity reaction in anaesthesia could be classified as IgE-mediated reactions only taking into account the result of tryptase determination. Although tryptase is found in both basophils and mast cells, concentrations in the former are 100–1000 times lower than in mast cells. In those reactions where elevated histamine but not tryptase is detected, this could be due to the intervention of basophils in the reaction instead of mast cells or due to the non-specific release via a non-immunologic mechanism [23]. It has been suggested that the differences in

Table 3. Number of patients presenting elevated serum tryptase depending on different cut-off points and the mechanism of reaction

Mechanism of reaction (n = 37)	Elevated tryptase according to different cut-off points and mechanism of reaction									
	Tryptase exceeds twice basal value* [7]		5 µg/L		8.23 µg/L [7]		> 10.5 µg/L [8]		> 11.4 µg/L	
	Yes	Not	Elevated ≥ 5	Normal < 5	Elevated ≥ 8.23	Normal < 8.23	Elevated ≥ 10.5	Normal < 10.5	Elevated ≥ 11.4	Normal < 11.4
IgE	10	8	15	4	11	8	8	11	7	12
Non-IgE	0	14	8	10	1	17	1	17	1	17

*In five patients, determination of baseline tryptase was not available.

tryptase concentrations in peripheral blood following an adverse reaction could depend on the type of mast cells stimulated and could be lower in reactions with greater cardiovascular involvement. Furthermore, tryptase could be normal in less severe reactions or when the blood sample has been extracted too soon [23]. In two of the cases in our series who only presented mucocutaneous symptoms (urticaria/angioedema) in whom an IgE-mediated mechanism was detected, elevated tryptase was not found, probably because the reactions were mild.

Moreover, it is important to diagnose IgE-mediated reactions, even though they are mild, as in future, more severe reactions may occur. If mild reactions were not studied, such as a simple exanthema with the idea that this type of reaction is due to the non-specific release of histamine caused by the anaesthetic agents used, a considerable number of IgE-mediated reactions would not be diagnosed.

Elevated plasma histamine in such a high percentage of patients suggests that it is participating in the reaction as has been widely shown in the literature [11, 19, 24]. Given its rapid clearance from the circulation, the blood sample must be taken in the first 15 min following the onset of the reaction. This represents a problem for the use of this test in the diagnosis of these reactions since when a severe reaction occurs, priority is given to treating the reaction and the extraction of blood may be delayed thus giving time for histamine to be cleared from the blood and thus leading to normal histamine levels being found. In any case, in some patients, persistently high levels of histamine in plasma may be found and this would be suggestive of maintained release.

No consensus exists in the literature as to the cut-off point that should be used to consider a tryptase result as elevated. Different publications use different cut-off points, which is somewhat surprising. The commercial company Thermo Fisher, for its ImmunoCAP technique recommends a cut-off point of 11.4 µg/L as this is the 95th percentile of its 129 control subjects. Other cut-offs reported in the literature are 8.23 µg/L [8] and 10.5 µg/L used by Schwartz [9]. It is important to highlight that these last two authors suggest that patients' baseline tryptase levels should also be taken into account.

In accordance with the results from our studies, using a cut-off point without taking baseline levels into account is not totally correct, as baseline levels higher than the cut-off point established can be found in some comorbidity, as occurred with our patient number 33 who suffered from chronic renal insufficiency and was in haemodialysis [25, 26]. For this reason in our study, we considered tryptase to be elevated in those cases in which patients' baseline values were doubled: it was the only criterion in which all the patients presented an IgE-mediated reaction.

However, our series was small and more studies with a greater number of patients are needed. For this reason, further studies should be performed to establish a minimum baseline tryptase level, to consider doubling as a criterion, as in patients with very low baseline levels, the very variability of tryptase levels at different times or the technique might lead to a doubling of values. We therefore believe that more studies should be carried out to determine from what exact tryptase level, twofold rising should be considered.

In conclusion, the determination of serum tryptase and plasma histamine is necessary and complementary tests, which help to confirm the presence of an immediate hypersensitivity reaction during an operation and provide some orientation about the mechanism involved. Levels of plasma histamine are very sensitive for diagnosing which symptoms correspond to an immediate hypersensitivity reaction and elevated tryptase levels correlate with positive skin tests and with an IgE-mediated mechanism. Not only a cut-off point of tryptase level, but also doubling baseline levels of tryptase could improve its discriminating potency between IgE- and non-IgE-mediated hypersensitivity reactions in anaesthesia.

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Conflict of interest

The authors declare no conflict of interests.

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