

BRIEF COMMUNICATION

Early skin testing is effective for diagnosis of hypersensitivity reactions occurring during anesthesia

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Abstract

Allergic skin tests have to be performed 4–6 weeks after an allergic anesthetic reaction. Patients with allergic reactions during anesthesia were prospectively included ($n = 44$). Skin tests were performed in two stages: (i) Stage 1 (S1), 0–4 days after the reaction; and (ii) Stage 2 (S2), 4–8 weeks after. Five (11.5%) surgical procedures were suspended due to the reaction. Positive skin tests were obtained in 25/44 patients (57%). Allergic diagnosis was carried out at S1 in 15/25 (60%) and at S2 in 10/25 (40%). Three patients resulted positive only in S1. Overall agreement among S1 and S2 skin tests was 70.45%. The kappa statistic was 0.41 (P -value = 0.002). Odds ratio of obtaining a false negative in S1 (compared with S2) was 3.33. Early allergological study is useful, could minimize false negatives, but should be considered as a complement to late skin tests.

Incidence of allergic reactions in perianesthetic settings varied from 1/1480 to 1/20000 (1, 2). Anaphylaxis can be IgE- or non-IgE-mediated. Intense degranulation of mast and/or basophil cells could explain negative skin tests (ST) in the following days or weeks (refractory period). Experts recommend ST be performed 4–6 weeks after the reaction (3, 4), but also recommend referring the patient for ST as soon as possible (5) or suggest the possibility to study the patient even immediately after a reaction in an emergency situation (6).

Early allergic study could be important when surgery is urgent (7).

The frequency of ST changing from negative to positive has not been studied, and the frequency of positive ST in early studies is unknown. We compared the results of ST performed two times in each patient: immediately and some weeks after a hypersensitivity reaction occurred during anesthesia.

Methods

Over a 4-year period (2008–2011), all immediate allergic anesthetic reactions (5) occurred in our Hospital were studied. Reactions were classified as mild (grade I), moderate (grade II), or severe (grade III or IV) (4).

Serum tryptase (ImmunoCAP FEIA; Phadia, Uppsala, Sweden) and blood histamine (8, 9) were determined at the moment (first 30 minutes) of the reaction, 2 and 24 h later.

ST were performed in two stages: during the first 0–4 days after the reaction (S1); and second, 4–8 weeks after the reaction (S2). Antihistamines were avoided by the anesthetist in the treatment of the reaction. Histamine (10 mg/ml for prick, 0.1 mg/ml for intradermal) and serum saline were used as controls.

Drugs used were tested at concentrations recommended (1). When prick tests were negative, intradermal tests were performed. Positive ST were considered with a size wheal 3×3 mm for prick and 5×5 mm for intradermal test, only if there were also pruritus and erythema. Ten nonexposed controls were tested when we had doubts about a possible false-positive result. Reactions were classified as IgE-mediated, when ST resulted positive with at least one drug or product; and non-IgE-mediated, when ST resulted negative.

Reproducibility was measured by overall agreement and Cohen's kappa statistic and proportions were correlated using McNemar's test; $P < 0.05$ were regarded as significant

(Stata software, version 12.0; StataCorp LP, College Station, TX, USA). The study was approved by local ethics committee and all the patients signed an informed consent form.

Results

From 67 patients that suffered an allergic reaction during anesthesia, 23 (34%) could not come 4–8 weeks after the reaction, and 44 (52% male; 12–82 years old, mean 43) were studied two times and were included. The reactions occurred during anesthetic induction in 26 patients (59%), during surgery in 9 patients (20.5%), and in the recovery unit in 9 patients (20.5%). Twenty-four reactions (54.5%) were mild, 10 (22.7%) moderate, and 10 (22.7%) severe. Five (11.5%) surgical procedures were suspended due to the severity of the reaction.

ST were positive in 25/44 patients (56.9%) and negative in 19/44. Tryptase was elevated in nine (20%): 9/25 IgE-mediated and 0/19 non-IgE-mediated reactions. Plasma histamine was elevated in 21/21 IgE-mediated and in 16/19 non-IgE-mediated reactions. The histamine result of 4 patients was lost.

The causative agent for IgE-mediated reactions was a drug in 22/25: 6 muscle relaxants, 5 antibiotics, 4 analgesics, 7 other drugs; one patient had cold urticaria (10); two were allergic to latex (Table 1).

About skin tests, 15/25 patients showed positive ST in S1; 22/25 showed positive ST in S2; 12/25 showed positive ST in both S1 and S2; 3 patients (2 atracurium, 1 chlorhexidine) showed positive ST only in S1; and 10 patients showed positive ST only in S2. Allergic diagnosis was carried out at S1 in 15/25 (60%) and in 10/25 patients (40%) at S2.

The overall agreement among results of S1 and S2-ST was 70.45%, and the kappa statistic was 0.41 (P -value = 0.002). Odds ratio of obtaining a false negative in S1 (compared

with S2) was 3.33. The P -value of 0.0923 from exact McNemar's test was not statistically significant.

There were no differences in serum tryptase, plasma histamine, or severity of the reactions between patients diagnosed at S1 or S2. Table 2 shows the results of the early studies according to the day after the reaction it was performed.

Discussion

The severity of an allergic reaction in anesthesia induction could lead to surgery being suspended. When the surgery cannot be delayed, the allergist will be asked to make a recommendation about the drugs that should be avoided or those that could be used. Data from our study showed a high percentage (60% of those with IgE-mediated reactions) of positive results in ST performed during the first 4 days after the reaction. Moreover, 3 patients (6.8%) diagnosed in the early study were negative at S2 and thus would not have been correctly diagnosed if only the S2 study had been performed. Other study found 79% positive ST or specific IgE to hymenoptera venom during the first 7 days after the reaction and two patients had negative ST 4–6 weeks after (11). In these patients, we can assume that specific IgE disappeared from the serum during the short period of 1 or 2 months, given that half-life of IgE is 2 days (12).

Moreover, in most of our patients, it was easier to perform S1 than S2: 34% who suffered a reaction did not return to the Allergy department 4–8 weeks after.

Recently, Soetens et al. (13) reported three cases in which ST were performed within 3 weeks after the anaphylactic reaction. They highlighted the need for a protocol of how to act if urgent surgery is necessary. Evidently, the knowledge of the sensitivity and percentage of false-negative results in early ST is the first step.

The mechanisms underlying the refractory period continue to be unknown, but could be related to the consumption of mediators from mast cells and basophils (1). IgE consumption during the reaction has not been demonstrated (14, 15).

In conclusion, the relative moderate strength of agreement between S1-ST and S2 seems to warrant an early allergological study in patients with an allergic reaction during an anesthetic procedure that could also minimize false negatives in the late study. However, early studies should not be considered as a replacement for, but as a complement to, late ST.

Table 1 Etiologic agents and number of patients that resulted positive in early (S1) and late (S2) studies respectively ($n = 25$)

	Positive in early skin testing (S1)	Positive only in late skin testing (S2)	Total
Atracurium	3	1	4
Amoxicillin/amoxicillin clavulanate	1	3	4
Cephazolin	1	0	1
Cisatracurium	1	1	2
Clorhexidine	1	0	1
Cold urticaria	1	0	1
Gelatin plasma expander	1	1	2
Iodine povidone	1	0	1
Latex	1	1	2
Morphine	0	1	1
Metamizole	3	1	4
Ondansetron	0	1	1
Protamine	1	0	1
Total	15	10	25

Table 2 Results of allergic study (early and late) according to the day after the reaction S1 study was performed

	Days after the reaction when S1 study was performed					Total
	0	1	2	3	4	
IgE-mediated diagnosed in S1	0	7	4	2	2	15
IgE-mediated diagnosed in S2	0	8	2	0	0	10
Non-IgE-mediated	1	13	3	2	0	19
Total	1	28	9	4	2	44

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Author contributions

A. Lafuente contributed to the study design, the patients selection and enrollment, and drafting the manuscript. G. Javaloyes participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript. F. Berroa participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript. M.M. Goikoetxea participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript. R. Moncada contributed to the enrollment of patients and drafting the

manuscript. J.M. Núñez-Córdoba participated in the analysis and interpretation of data and drafting the manuscript. P. Cabrera participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript. C. D'Amelio participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript. M.L. Sanz contributed to the study design and allergological study. G. Gastaminza performed the study design, participated in the patients selection and enrollment, allergological study, analysis and interpretation of data, and drafting the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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