

Clinical evaluation of *in vitro* leukocyte histamine release in allergy to muscle relaxant drugs

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We have evaluated the *in vitro* leukocyte histamine release tests for the diagnosis of allergy to muscle relaxant drugs in 40 patients (Group A) and a control group of 44 subjects with negative leukocyte histamine release (Group B). Non-IgE dependent histamine release, expressed as a percentage of the total blood histamine, was $3.94\% \pm 0.49$ in Group B. The upper limit of positivity was estimated to be 5% (mean + 2 SD). Leukocyte histamine release tests were positive in 65% of the patients from Group A. The concordance between LHR and QAS-RIA was 64%. The maximal histamine release was observed at dilutions of 10^{-2} – 10^{-4} in 20 of the 26 positive cases. The maximal histamine release was $43.8\% \pm 23.3$. The spontaneous histamine release was as low as $1.7\% \pm 1.1$. Cross-reactivity among the 5 different muscle relaxant drugs has been investigated and compared by intradermal testing. The muscle relaxant drugs which gave the lower skin reaction (M2) and the drug responsible for shock (M1) were selected for the study of *in vitro* leukocyte histamine release. Of 20 patients, 10 had, simultaneously, a positive test to M1 and a negative to M2. All of the 10 cases had negative ID tests with M2. Three of these patients subsequently underwent general anesthesia with the muscle relaxant chosen as harmless (M2) without any clinical reaction.

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The incidence of anaphylactoid reactions during anesthesia is estimated to approximately one case in 5000 general anesthetics and mortality is 6% (6, 11). Muscle relaxant drugs are responsible for 51% of these incidents (16). A recent study made in France of 2 500 000 general anesthetics mentions the muscle relaxants as responsible for 81% (28).

Adverse reactions to muscle relaxants are mostly due to an IgE-mediated mechanism. Presence of serum-specific IgE against myorelaxants in the sera of drug-sensitive subjects was first demonstrated by Baldo & Fisher (3, 4, 5). The IgE antibodies binding the site of the drugs involve quaternary ammonium compounds, and all molecules of the muscle relaxants present at least one quaternary ammonium group. This explains the cross-reactivity that exists among these drugs (4, 10, 14, 15, 28).

At least 2 quaternary ammonium groups are needed to elicit the release of mediators from basophils. Leukocyte histamine release in the presence of soluble muscle relaxants has been studied by several

authors who conclude that mediator release corresponds to a specific immunological mechanism (1, 38, 40, 42).

Diagnosis of allergy to muscle relaxants is now established mainly by clinical history, skin tests and detection of specific IgE antibodies. Leukocyte histamine release tests (LHR tests) are seldom used, the main reason being the difficulty of carrying them out.

Recently, a new radioimmunoassay (RIA) for histamine has been developed. This new method is specific, since the monoclonal antibody selected does not recognise biological amines other than histamine (23, 30, 35). Due to its high sensitivity the LHR test can be carried out with small volumes of whole blood in presence of soluble allergens, and the released histamine measured by RIA, thus obviating isolation or concentration of leukocytes.

In this study we have evaluated the LHR test with whole blood for the diagnosis of allergy to muscle relaxants. We have also compared this test with the

2 other diagnostic tests currently used, skin tests and specific IgE radioimmunoassay.

Material and methods

Group A comprised 40 patients (35 women and 5 men) with age range from 21 to 64 years. The selection criterion was a reported adverse reaction to a muscle relaxant under general anesthesia. The diagnosis of allergy to muscle relaxant drugs was established from the clinical history, skin testing and QAS-RIA in 33 cases; the remaining 7 had negative QAS-RIA. The muscle relaxants responsible for shock (M1 in our study) were suxamethonium, vecuronium, pancuronium, alcuronium and gallamine in 14, 12, 5, 4 and 5 cases, respectively.

Group B comprised 44 subjects presenting negative LHR tests to different muscle relaxants: suxamethonium, vecuronium, pancuronium, alcuronium, gallamine and atracurium in 7, 18, 8, 3, 5 and 3 cases, respectively, and served as control group. Atracurium was included since it is considered to elicit non-immunological histamine release. The upper normal limit of positivity was estimated from these 44 LHR tests and corresponded to the mean $\pm$ 2 SD of the percentage of histamine release.

The 40 patients in Group A underwent intradermal skin tests (ID tests) and prick skin tests to muscle relaxant drugs, as described elsewhere (9, 19, 24). For ID tests, standard commercial solutions of suxamethonium, vecuronium, pancuronium, alcuronium, atracurium and gallamine were diluted in phenolic isotonic saline up to the concentrations indicated in Table 1. Cross-reactivity was investigated in 20 patients by intradermal testing to 5 muscle relaxants at increasing concentrations in order to establish which drug gave the lower reactivity (M2). Reactions were read 15 min after injection and considered positive when the wheal was > 10 mm. Prick tests were performed on the forearm using undiluted substances. Reactions were read after 15 min and considered positive when the wheal was > 3 mm or 50% of the codein positive control.

For sample collection 2 ml blood was collected in a heparinized tube according to Lorenz's instructions (21). Briefly, when histamine release did not occur immediately, the blood sample was stored at 4°C for a maximum of 4 h.

In vitro leukocyte histamine release. The RIA of histamine was performed using the method of Immunotech (Luminy, France) following the manufacturer's instructions. The within-run variation coefficient of this RIA was estimated using 2 samples with a low and a high concentration of histamine, respectively. All 40 blood samples were tested for histamine release in the presence of the muscle relaxant responsible for shock (M1) and 20 of them were tested in the presence of 2 different muscle relaxants, M1 and M2. Fifty μ l of whole blood was needed for the quantification of total histamine. Cell lysis was achieved by dilutions of 1/20 in water and freeze-thawing. The remaining blood was diluted to 1/4 in the N'-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid-tyrode's buffer (histamine release buffer, supplied by Immunotech, Luminy, France).

The test was performed with 200 μ l of the diluted blood in presence of 100 μ l of 5 dilutions ranging from 10^{-1} to 10^{-5} of the muscle relaxant drugs. Dilutions were prepared as for ID tests but using histamine release buffer as diluent of the commercial stock solutions (Table 1). The samples were incubated for 30 min at 37°C. The reaction was stopped by cooling the tubes down to 4°C. After centrifugation at 1000 rpm for 10 min at 4°C, the supernatant was recovered and assayed for histamine.

The histamine-RIA is based on competition between acylated histamine and labelled acylated histamine for binding to monoclonal antibody-coated tubes. Each supernatant (100 μ l) was acylated with the acylation reagent (supplied by Immunotech) in an alcalin medium (borate buffer pH = 8.2). The tubes were vortexed until complete solubilization of the acylation reagent. This acylation step is essential for immunorecognition of histamine. We then incubated 50 μ l of acylated samples or standards with 500 μ l of iodinated tracer in antibody-coated tubes at 4°C for 18 h minimum. The tubes were aspirated and counted in a gamma counter.

Results of LHR tests (Hi) were expressed as a percentage of total histamine content (Ht) of the sample after correction for spontaneous release (Ho) from control tubes, using the following formula:

$$HR = \frac{Hi - Ho}{Ht - Ho} \times 100$$

Table 1. Concentration (μ mol/l) of muscle relaxant drugs at the different dilutions used for skin testing and LHR tests

Dilution	Altracrium	Suxamethonium	Gallamine	Aluocuronium	Pancuronium	Vecuronium
10^{-1}	800	2000	2200	700	270	600
10^{-2}	80	200	220	70	27	60
10^{-3}	8	20	22	7	2.7	6
10^{-4}	0.8	2	2.2	0.7	0.2	0.6
10^{-5}	0.08	0.2	0.2	0.07	0.02	0.06

Quaternary ammonium sepharose radioimmunoassay. Detection of specific anti-muscle relaxant IgE was done by the QAS-RIA method described elsewhere (12, 13).

Results

The within-run variation coefficient of the radioimmunoassay for histamine shows similar results to those stated by the manufacturer with a variation coefficient of 8.3% and 12.4 for high and low concentration samples, respectively.

The non-IgE-dependent histamine release, expressed as a percentage of the total blood histamine in our control group (Group B), was $3.74\% \pm 0.56$. The upper limit of positivity was estimated to be 5% (mean + 2 SD) (Table 2).

The LHR in presence of M1 was positive in 26 of the 40 patients, corresponding to a sensitivity of 65%. By comparison, the concordance between the skin tests and the QAS-RIA was 82.5%.

The maximal histamine release was observed at dilutions of 10^{-2} – 10^{-4} in 20 cases (Fig. 1) and the mean maximal histamine release was $43.8 \pm 23.3\%$ (extreme values were 5% and 100%). The number of positive LHR versus the total number of tests was 7/14 for suxamethonium, 9/12 for vecuronium, 3/5 for pancuronium, 3/4 for alcuronium and 4/5 for gallamine (Fig. 2).

All patients with positive LHR tests also had a positive ID test for the drug responsible for the anaphylactic reaction. The intradermal tests were positive at dilutions from 10^{-3} to 10^{-5} in 23 of the 26 cases with positive LHR tests. The other 3 cases with positive LHR corresponded to an ID positive at a dilution of 10^{-2} (Fig. 3). In 20 patients, we compared the results of the LHR tests obtained with the muscle relaxant (M1) incriminated in the anaphylaxis (from clinical data and positive skin tests) to the results obtained with a second muscle relaxant (M2), which gave lower skin reactivity (Fig. 4).

Table 2. Mean values $\pm$ SD of histamine release obtained in the 44 control subjects

(n=44)		
Dilution	Mean $\pm$ SD	Mean + 2 SD
Ho	1.53% $\pm$ 0.92	3.37
10^{-1}	1.55% $\pm$ 1.11	3.78
10^{-2}	1.82% $\pm$ 1.33	4.48
10^{-3}	1.59% $\pm$ 0.81	3.21
10^{-4}	1.73% $\pm$ 1.31	4.35
10^{-5}	1.51% $\pm$ 0.88	3.27
		3.74% $\pm$ 0.56

Each mean value corresponds to 44 values obtained with each dilution. Ho basal plasma histamine. The upper limit of control values was estimated from the mean + 2 SD

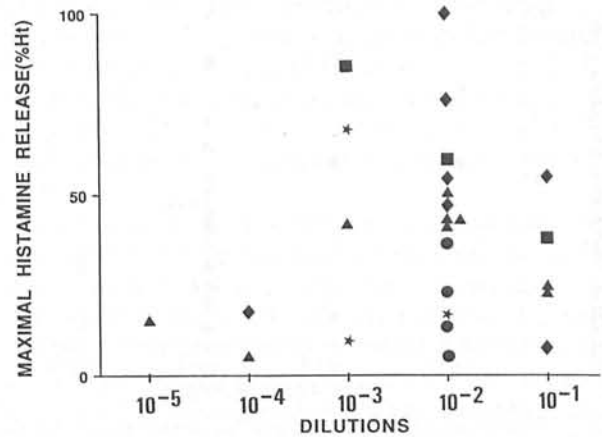


Fig. 1. Dilution at which maximal histamine release was obtained for each of the 26 positive LHRs. Released histamine was expressed as a percentage of total blood histamine (% Ht). Muscle relaxants tested were: suxamethonium (◆), vecuronium (▲), pancuronium (*), gallamine (●), alcuronium (■).

LHR was positive for M1 and negative for M2 in 10 cases.

The concordance between LHR and QAS-RIA was 64% (21 positive LHR/33 positive QAS-RIA). The QAS-RIA was positive and concordant with clinical history in 12 discordant cases with negative LHR tests. Of the patients with positive LHR 81% also had a positive QAS-RIA (21 concordant cases/26 positive LHR). The LHR tests were positive and concordant with clinical history in 5 concordant cases with negative QAS-RIA.

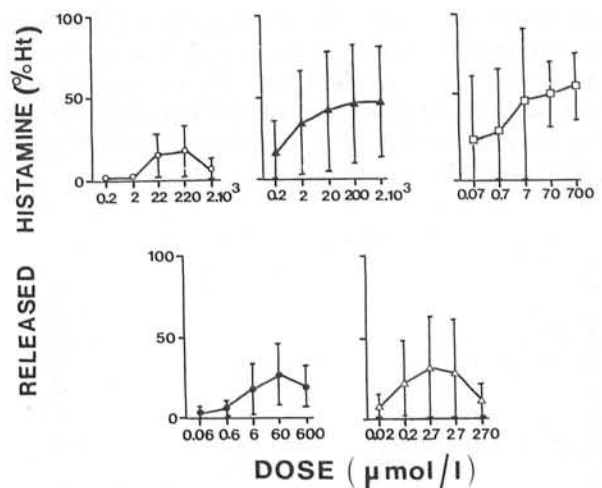


Fig. 2. Histamine released, expressed as a percentage of total blood histamine (% Ht), for the 26 positive LHR in presence of increasing concentrations (μ mol/l) of muscle relaxant drugs. Muscle relaxants tested were: gallamine ($n=4$, ○), suxamethonium ($n=7$, ▲), alcuronium ($n=3$, □), vecuronium ($n=9$, ●), pancuronium ($n=3$, △). Each point represents the mean values and the bars represent the standard deviation.

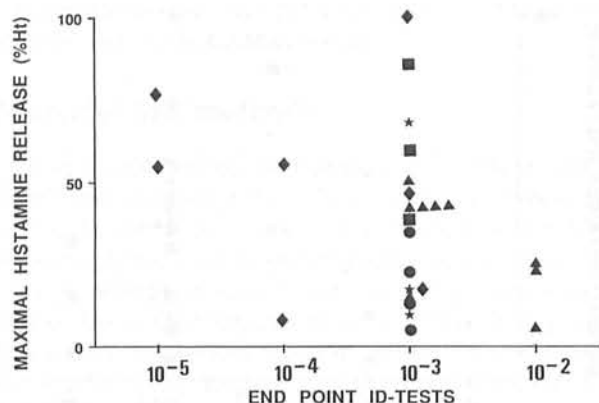


Fig. 3. Relationship between maximal histamine release and the end-point dilution for ID tests in 26 positive LHRs. Muscle relaxants tested were: suxamethonium (◆), vecuronium (▲), pancuronium (*), gallamine (●), alcuronium (■).

Discussion

Until now the protocols for LHR tests were too complicated for routine use. Large amounts of blood were needed and basophils had to be isolated by dextran sedimentation and concentrated (8, 21). Measurement of the released histamine was usually performed by fluorometry (33), high-performance liquid chromatography (HPLC) (32), or a radio-enzymatic method (34). We performed our tests with 2 ml of whole blood instead of isolated cells, thus keeping close to physiological conditions.

It should be emphasized that LHR tests need appropriate sample handling (21). When this is the case the spontaneous histamine release is always under 5% of total histamine content (Ht) of the sample. In our study, the mean value of spontaneous histamine release in Group A was as low as $1.66\% \pm 1.1\%$ of Ht (extreme values ranging from 0.4% to 4.7%). The spontaneous histamine release was similar to that observed in the control group ($1.53\% \pm 0.92$).

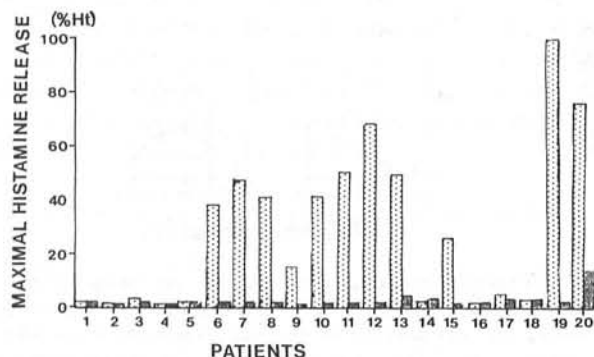


Fig. 4. Maximal histamine released from leukocytes in presence of 2 different muscle relaxants, M1 (.....) and M2 (■), in 20 patients.

Since the histamine content in human blood runs parallel to the number of basophils, results could be influenced by the number of basophils/ml blood (20). To avoid this, results are referred to the total histamine content of the sample. Nevertheless, interpretation of results must take account of the blood histamine levels, since a sample with high Ht may be responsible for false negative results. The mean values $\pm$ SD of total histamine content (Ht) were 448.9 ± 203.7 nM in 40 samples, with extreme values ranging from 981 nM to 145.5 nM. The total histamine content was similar to that observed in the control group (437.2 ± 327.7 nM).

LHR tests must be done 6–8 weeks after the incident in order to avoid false negative results, since a refractory period has been observed during which basophils do not react even though specific IgE can be detected (8, 41).

It is established that muscle relaxant can induce *in vitro* IgE-dependent histamine release from the patient leukocytes and that no histamine release can be induced from leukocytes of control subjects (2, 8, 37, 42). Fig. 2 shows that drug excess caused inhibition of histamine release, as observed with high molecular weight antigens. This phenomenon may be due to monovalent binding of the quaternary ammonium groups onto IgE (1).

The role of quaternary ammonium groups in the triggering of mediator release from sensitized cells has recently been studied by Didier et al. They showed that histamine released from patient leukocytes can be specifically induced by aliphatic diammonium structures (7). In general, at least 2 quaternary ammonium groups are needed in the structure to elicit histamine release. This is so in the drugs we tested, except for vecuronium which shows a single quaternary ammonium substitute. However, clinical reactions to vecuronium have been reported (25, 29, 41). Moreover, we have obtained positive LHR tests with vecuronium in 9 of 12 tests (75%). Several hypotheses could explain such a phenomenon. The second ammonium of vecuronium which is a tertiary, could become almost completely protonated at physiological pH. The drug will then share 2 cationic groups. The protonated tertiary nitrogen may have a binding capacity for IgE antibodies of blood basophils and tissue mast cells (1). Another hypothesis is that vecuronium may form oligomers and act as a hapten in whole blood.

The sensitivity of LHR tests for the diagnosis of muscle relaxant allergy is estimated at 65% in our study. This is higher than the 53% sensitivity estimated by Laroche et al. (17). In contrast, higher sensitivities have been reported by other authors: 83% and 90% for Vervloet et al. and Facon et al., respectively (8, 40). However, the patient series of these 2 studies were much smaller. Both of them

practised muscle relaxant LHR tests with isolated basophils incubated with suxamethonium, and measured the released histamine by a fluorometric assay. The differing results cannot be explained by the different methods used to measure the released histamine, since the sensitivity of the fluorometric assay is lower than that of RIA. Vervloet et al. added DO2 to the release buffer in order to increase sensitivity. This group found a sensitivity of 37% when no DO2 was added. Only one muscle relaxant was used in these studies; therefore the specificity of LHR tests was not studied.

Recent studies have shown the usefulness of skin tests and QAS-RIA for detecting the presence of specific IgE in adverse reactions to muscle relaxants (9, 12, 13, 18, 27, 39). In the present study, the sensitivity of QAS-RIA was estimated at 82.5% and was therefore significantly higher than that of LHR. The QAS-RIA explored only the circulating specific IgE. The presence of specific IgE in serum is not sufficient to predict or to explain a clinical adverse reaction to the drug. On the contrary, LHR tests investigated the reactivity of basophils. The lower sensitivity of the LHR tests, as compared with QAS-RIA, could be explained in part by unresponsiveness of basophils in some of the patients. This unresponsiveness is independent of whether the person has an allergy or not. A good way to improve the LHR test could be to test, systematically, the histamine release of basophils in the presence of anti-IgE.

The main problem of allergy to muscle relaxants comes from the existence of cross-anaphylaxis. Cross-reactivity between muscle relaxants was suggested by skin tests (10, 26, 36) and demonstrated by RAST inhibition studies (14, 15). Cross-reactivity studied by ID tests is present in 84% of individuals, but only 10% show cross-reactivity to all the muscle relaxants (25, 31). In a comparative study of both techniques, less cross-reactivity was shown by ID tests than by QAS-RIA (13). This may be because factors other than the existence of IgE antibodies play a part in allowing the bridging of IgE. It would be of benefit if the safety of a muscle relaxant could be predicted. Immunological tests are needed for choosing a safe muscle relaxant when muscle relaxants in allergics are unavoidable. A safe muscle relaxant should give lower skin reactivity in ID tests, and M2 and M1 should be tested for *in vitro* leukocyte histamine release simultaneously. Our data, illustrated in Fig. 4, prove that LHR test is an efficient method to evaluate the risk of clinical cross-reactions between different muscle relaxants. Of 20 patients in whom we had studied the LHR with 2 different muscle relaxants, 10 had, simultaneously, a positive LHR to M1 and a negative to M2. Three of these patients subsequently underwent general anesthesia with the muscle relaxant chosen as safe (M2) without any

clinical reaction. These promising results need confirmation by a study with a larger population before proposing ID tests and LHR as the 2 methods for selecting M2 in a subsequent anesthesia. In addition, a negative LHR for M2 can only be considered a valuable result if a simultaneous LHR was positive for M1.

In conclusion, a combination of clinical history, skin testing and detection of specific IgE by QAS-RIA is required for the diagnosis of allergy to muscle relaxants. The LHR tests are needed for choosing safe muscle relaxant. A positive LHR test for M1 and a negative for M2 is a good indication for using M2 in a subsequent anesthesia when the patient also shows a negative ID test for M2. These studies must be undertaken for each patient individually since no general conclusions can be made.

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