Erciyes Med J 2023; 45(1): 25–31 • DOI: 10.14744/etd.2022.80633

ORIGINAL ARTICLE – OPEN ACCESS

Assessment of CD63 and CD203c Basophil Activation Tests in Patients with Immediate Drug Hypersensitivity Reaction to Rocuronium

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ABSTRACT

Objective: Neuromuscular blocking agents (NMBA) are commonly used in general anesthetic applications, and are responsible for more than half of all anaphylactic reactions during general anesthesia. The aim of this study is to investigate the contribution of BasophilActivation Test (BAT) to the diagnosis in patients who developed an immediate drug hypersensitivity reaction due to rocuronium.

Materials and Methods: The study included 10 patients who developed urticaria and/or angioedema following rocuronium administration during anesthesia. Hypersensitivity to rocuronium was assesed with BAT including CD63 and CD203c expression analysis of blood samples by flow cytometry at least one month after the reactions.

Results: All patients were found positive for CD63 expression at the drug dilutions of 0.01 and 0.1 mg/ml, while nine (90%) patients were positive at the drug dose of 1 mg/ml. When assessing the CD203% expression at different drug dilutions, seven (70%) patients were found to be positive at the drug dilutions of 0.01 and 0.1 mg/ml, while eight (80%) were positive at the drug dose of 1 mg/ml.

Conclusion: This study has demonstrated that BAT can be used for diagnostic purposes in immediate drug hypersensitivity reactions to NMBA like rocuronium. The present study, to the best of our knowledge, is the first to assess the diagnostic significance of BAT in immediate drug hypersensitivity reactions caused by rocuronium in our country.

Keywords: Basophil activation test, Rocuronium, Hypersensitivity, Drug allergy, CD63, CD203c

Cite this article as:
Doğruel F, Canpolat DG, Özsoy S, Rıhtım T, Köker MY, Yılmaz İ. Assessment of CD63 and CD203c Basophil Activation Tests in Patients with Immediate Drug Hypersensitivity Reaction to Rocuronium. Erciyes Med J 2023; 45(1): 25-31.

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Submitted
17.02.2022

Revised
20.03.2022

Accepted
21.06.2022

Available Online
28.11.2022

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INTRODUCTION

Neuromuscular blocking agents (NMBA) are drugs that are widely used in general anesthesia applications. Immediate drug hypersensitivity reactions can develop against NMBAs, which are necessary in both endotracheal intubations and surgical interventions. Such reactions are most commonly associated with non-depolarizing neuromuscular blocker agents (NNMB) at a rate of 58.2%–61.6%. The hypersensitivity reactions associated with NNMBs are linked to rocuronium in 43.1% of cases, although this rate varies according to the frequency of use of the drug (1, 2). Rocuronium is an intermediate-acting NNMB in amino-steroid structure used in general anesthesia. The allergic reactions associated with this agent have been linked to the quaternary ammonium group included in its structure (3, 4).

The diagnosis of allergic reactions to NMBA is not always straightforward, so there is considerable interest in the identification of reliable diagnostic tools. While drug provocation testing is the standard approach to the identification or exclusion of allergies, there is a significant associated risk, and it is not possible to apply such tests in clinical practice. Although there is a risk of the development of allergic reactions during the application of skin tests with thee agents in patients with a history of serious anaphylaxis against the offending NMBAs (5–7), skin prick and intradermal tests may be used at appropriate concentrations (non-irritating doses). As such, there is a need to identify reliable diagnostic tools to circumvent these safety risks.

The importance of basophil activation test (BAT) – an in vitro diagnostic tool – in the diagnosis of immediate drug hypersensitivity reactions against drugs is currently increasing. The measurement of CD63 and CD203c expression, as markers of basophil activation, through flow cytometry is referred to as BAT.

The present study investigates the use of BAT – involving the measurement of CD63 and CD203c expression – for the diagnosis of immediate drug hypersensitivity reactions against rocuronium at 10 patients experienced such reactions.

MATERIALS and METHODS

Study Population

Ten patients developing an urticaria and/or angioedema within 1–2 min after rocuronium administration during general anesthesia in the Department of Oral and Maxillofacial Surgery of the Faculty of Dentistry of Erciyes University be-

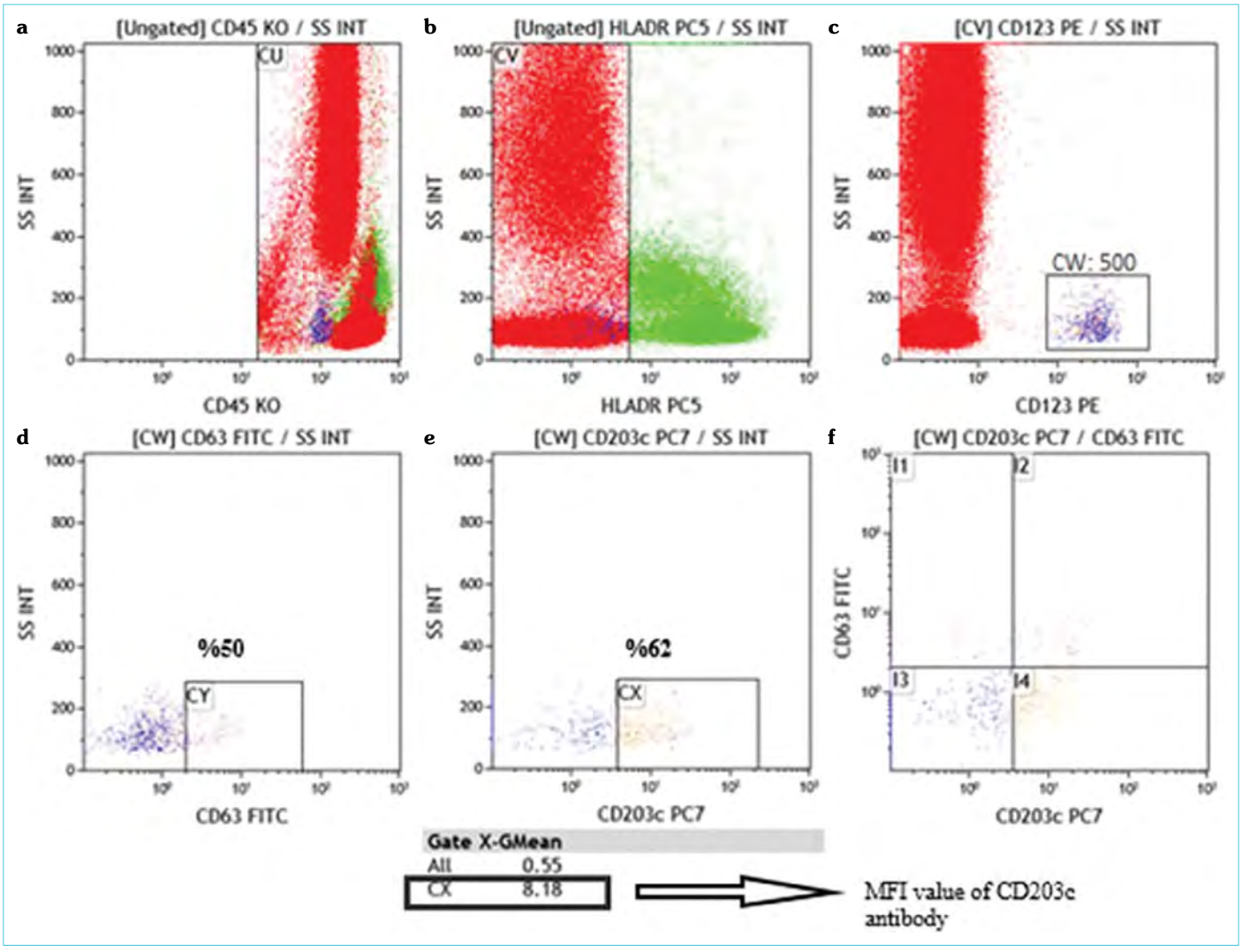

Figure 1. Analysis of basophil cells in the drug allergen (0.01 mg rocuronium) tube of Patient 1 through flow cytometry and a gating strategy

tween March 2017 and April 2019 were included in the single-center study. The patients, not having any drug allergies or a history of other known allergies, did not use any medication before surgery. Patients with skin findings after rocuronium were observed in the operating room by the same anesthesiologist. There were only skin/mucosa findings in the patients, no other system involvement was present. The patients, in a study protocol that was approved by the Erciyes Medical School Ethic Board (number: 2017/145) and in accordance with the Declaration of Helsinki, signed informed consent forms documenting their understanding of the procedures and this research.

In a percentage of CD63 and CD203c expression that was measured by flow cytometric analysis, heparinized venous blood in 3 ml from patients with rocuronium hypersensitivity was tested for basophil activation test at drug dilution doses (0.01 mg/ml, 0.1 mg/ml, 1 mg/ml). The research was carried out at Immunology Department of Erciyes Medical School.

Materials

Immunophenotyping and Stimulation of Basophils

Monoclonal antibodies CD45-PC5, CD63-FITC, CD123-PE, HLADR-ECD and CD203c-PC7, (Beckman Coulter, BC, Brea, CA, USA) were used for basophils immunofhenotying. We used N-fMLP (f-Met-Leu-Phe) as stimulant for basophil activation in positive control and phosphate buffered saline (PBS) in negative control.

BAT

The BAT procedure for the measurement rocuronium effect is described in detail elsewhere (8, 9). In summary, the blood samples were dispensed in 2 aliquots into positive control tubes (N-fMLP, anti-IgE) and 1 tubes in negative control (PBS) and 3 rocuronium dilutions, at a concentration of 0.01 mg/ml, 0.1 mg/ml, and 1 mg/ml were added in an experiment in which patients were invited to the clinic at least one month after the operation and 3 ml of blood was drawn in a heparinized tube.

In basophil activation process, the samples were then incubated at 37 °C for 30 min. After incubation, the tubes were placed on ice for 5 min. Cooling on ice stopped the degranulation. Ten min lysis was applied to remove erythrocytes. It was centrifuged at 1000 rpm for 5 min. The supernatant was removed. Finally, 0.5 ml of isoflow was added to the tubes and suspended.

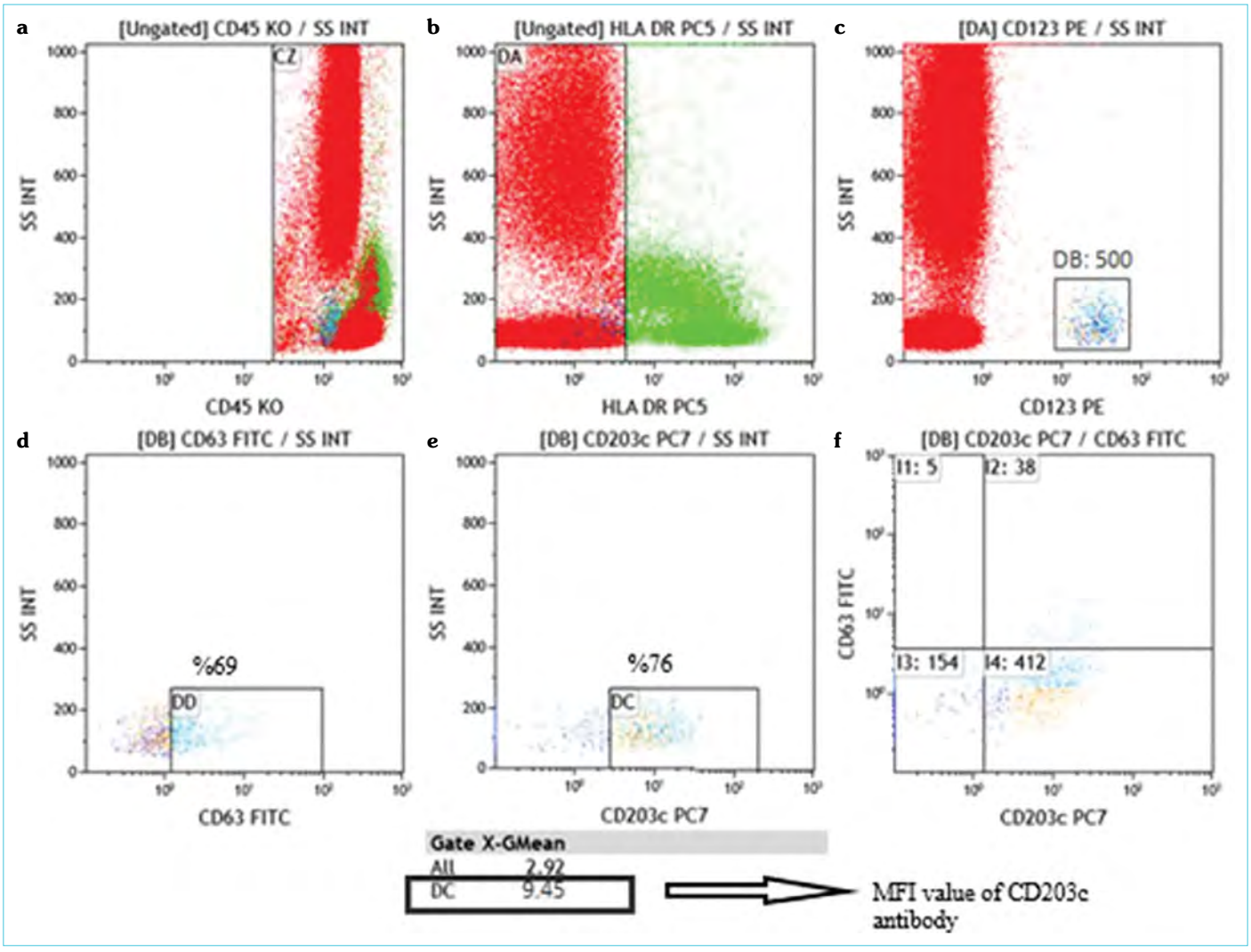

Figure 2. Analysis of basophil cells in the drug allergen (0.1 mg rocuronium) tube of Patient 1 through flow cytometry and a gating strategy

Flowcytometric Data Acquisition

The flowcytometric analysis identified 500 basophil cells out of one million (1×10^6) cells. Analysis was performed using Navios-EX (BC) flow cytometer device and Kaluza software program (BC). Basophils were defined as low side-scatter, CD123 positive and human leukocyte antigen (HLA)-DR negative cells, and the quantitative percentage determination of degranulated basophils was measured with CD63 and CD203c expression.

Analysis and Evaluation of BAT

The study was determined on the basis of significant upregulation of CD63 and CD203c on basophils (CD63 and CD203c/IgE -fMLP positive cells) in response to fMLP and anti-FceRIa antibody. Data were expressed as CD63, CD203c expression level, and CD203c mean fluorescence intensity (MFI) and for CD203 was MFI greater than or equal to 2 (10, 11). An increase of >5% in CD63-positive basophils was considered a positive result. The number of CD123+ cells, CD123+/CD63+ cells, and CD123+/CD203c+ cells per million cells was counted by flow cytometry.

Statistical Analysis

The patient data were transferred to a digital environment, where TURCOSA (Turcosa Analytics Ltd. Co., Türkiye, www.turcosa.com.tr) software was used for the statistical analyses. Normally distributed numerical data were expressed as the mean and standard deviation, and non-normally distributed data were expressed as the median, minimum and maximum, where the normal distribution of the data was tested with a histogram, q-q graphs and a Shapiro–Wilk test, and variance homogeneity was tested with a Levene test.

RESULTS

The basophil activation markers (CD63 & CD203c) of 10 patients, the mean age of which (8 female; 2 male) was 27±13,9 years, who had developed an immediate drug hypersensitivity reaction to rocuronium (urticaria and/or angioedema) were evaluated in the present study.

The method used to obtain the cell counts of Patient 1 in different drug concentrations through gating and analysis is shown in Figures 1, 2 and 3.

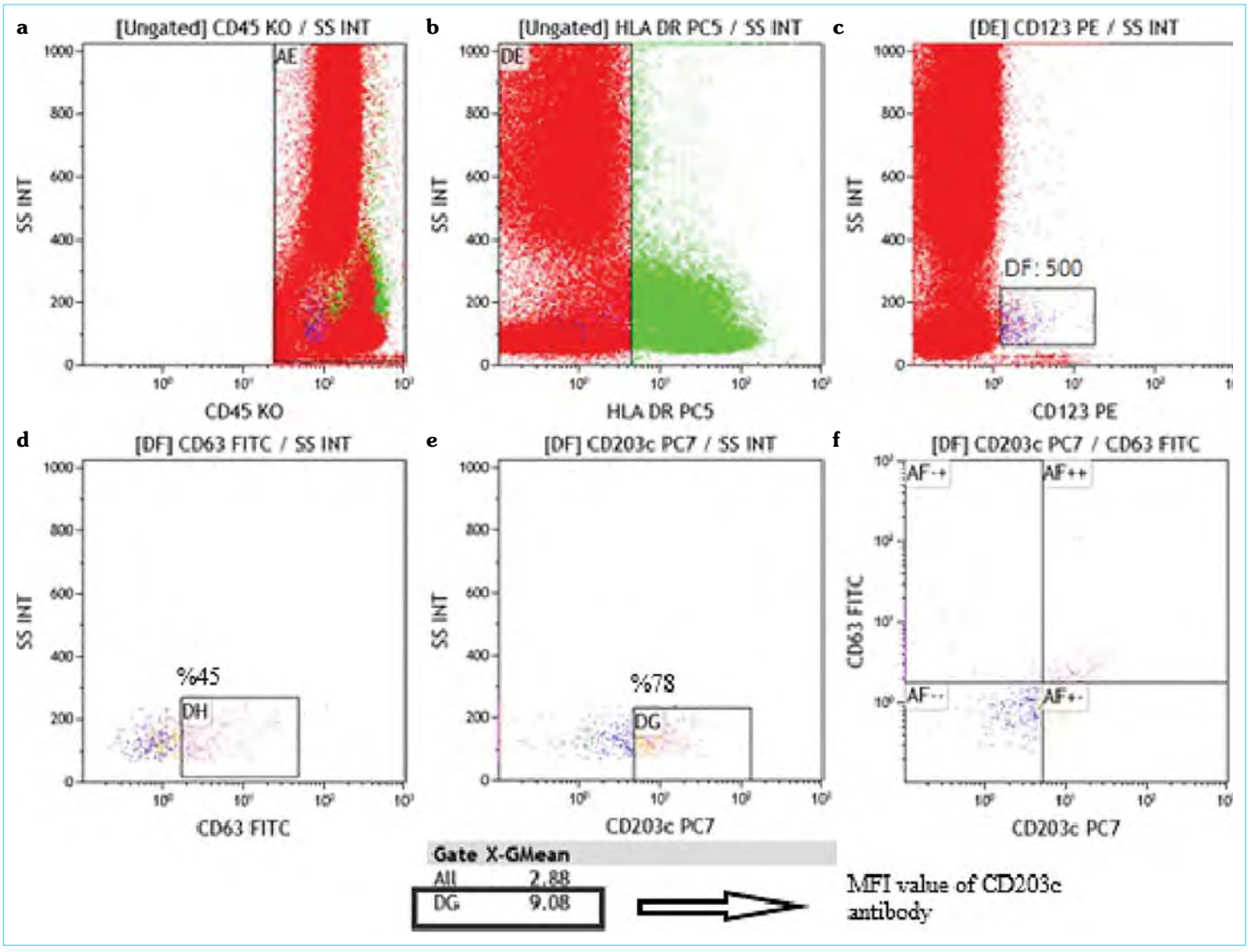

Figure 3. Analysis of basophil cells in the drug allergen (1 mg rocuronium) tube of Patient 1 through flow cytometry and a gating strategy

BAT Results

When the CD63% expressions of the patients were evaluated and compared with the negative control, positivity was found in the 0.01 and 0.1 mg drug dilutions, and nine patients were positive in the 1 mg drug dose (90%) (a 5% increase was accepted as positive). The mean % increase was 20.79%±10.1% in the 0.01 mg rocuronium drug dilution with a minimum increase of 9.08% and a maximum of 36.47%. The mean % increase was 28.6%±7.39% in the 0.1 mg rocuronium drug dilution with a minimum increase of 17.32% and a maximum of 42.93%. The mean % increase was 24.93%±13.18% in the 1 mg rocuronium drug dilution with a minimum increase of 4.59% and a maximum of 42.77% (Table 1, Fig. 4–6).

When assessing the CD203% expression in terms of % expression at different drug dilutions in comparison with the negative control, three patients were found to be negative for the drug dilutions of 0.01 and 0.1 mg, while two patients were negative for the drug dose of 1 mg (An increase of 5% was accepted as positive). The mean % increase was 16.29%±12.75% in the 0.01 mg rocuronium drug dilution with a minimum increase of 1.62% and a maximum of 33.61%. The mean % increase was 24.82%±14.63% in the 0.1 mg rocuronium drug dilution with a minimum increase of 4.29% and a maximum of 48.9%. The mean % increase was 32.97%±19.6% in the 1 mg rocuronium drug dilution with a minimum increase of 1.5% and a maximum of 59.06% (Table 2).

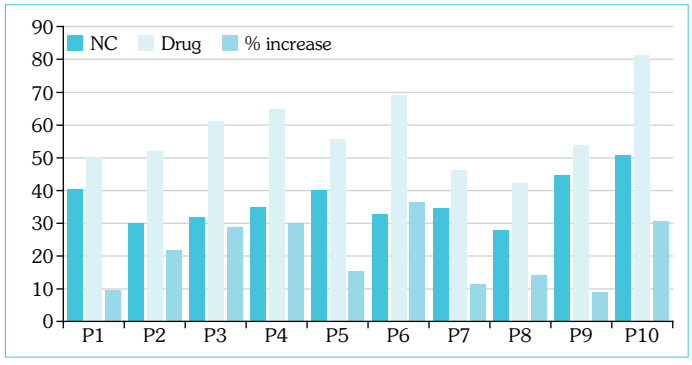

Figure 4. Displayed increase in CD63+ Cells in the 0.01 mg drug dilution when compared to NC

P: Patient; NC: Negative control

Table 1. Demonstration of CD63+ cells of the patients in different drug dilutions

Patients	NC(-)	PC(Anti-IGE)	PC(FMLP)	Drug dilution 0,01		Drug dilution 0,1		Drug dilution 1	
	%	%	%	%	% Increase	%	% Increase	%	% Increase
P1 CD63+	40.41	55	58	50	9.59	69	28.59	45	4.59
P2 CD63+	30	60	50	52	22	65	35	40	10
P3 CD63+	32	50.48	55	61	29	60	28	68.13	36.13
P4 CD63+	35	45	58	65	30	68	33	53	18
P5 CD63+	40.2	82	56	55.68	15.48	62.46	22.26	76.5	36.3
P6 CD63+	32.78	60.74	58.72	69.25	36.47	75.71	42.93	59.31	26.53
P7 CD63+	34.7	54.6	50.2	46.2	11.5	64.8	30.1	54.1	19.4
P8 CD63+	27.96	52.78	57.8	42.07	14.11	49.05	21.09	70.73	42.77
P9 CD63+	44.58	58.5	60.14	53.66	9.08	72.65	28.07	61.05	16.47
P10 CD63+	50.58	88.5	90.14	81.3	30.72	67.9	17.32	89.7	39.12

P: Patient; NC: Negative control; PC: Positive control

Table 2. Demonstration of expression of CD203+ cells of the patients in different drug dilutions

	NC(-) (n)	PC(Anti-IGE)	PC(FMLP)	Drug dilution 0,01		Drug dilution 0,1		Drug dilution 1	
	%	%	%	%	% Increase	%	% Increase	%	% Increase
P1 CD203c+	56.57	72	68	62	5.43	76	19.43	78	21.43
P2 CD203c+	50	56	60	61	11	72	22	75	25
P3 CD203c+	44.65	59.5	80.4	51.15	6.5	54.23	9.58	88.9	44.25
P4 CD203c+	45	56	60	70	25	79.2	34.2	78.12	33.12
P5 CD203c+	17.6	33.5	41.8	51.15	33.55	54.23	36.63	66.7	49.1
P6 CD203c+	36.65	26.8	18.68	12.14	–	25.54	–	41.04	4.39
P7 CD203c+	9.2	17.8	15.4	7.1	–	6.4	–	10.7	1.5
P8 CD203c+	2.4	1.35	78.9	4.02	1.62	6.69	4.29	61.46	59.06
P9 CD203c+	1.4	94.07	79.97	15.01	13.61	50.3	48.9	52.36	50.96
P10 CD203c+	41.4	84.07	79.97	75.01	33.61	65	23.6	82.36	40.96

P: Patient; NC: Negative control; PC: Positive control; n: Number

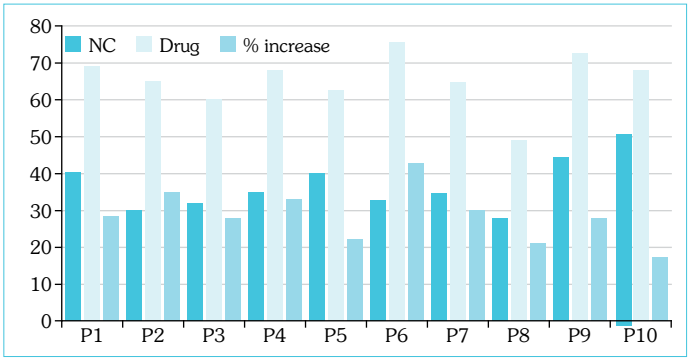

Figure 5. Displayed increase in CD63+ Cells in the 0.1 mg drug dilution compared to NC
P: Patient; NC: Negative control

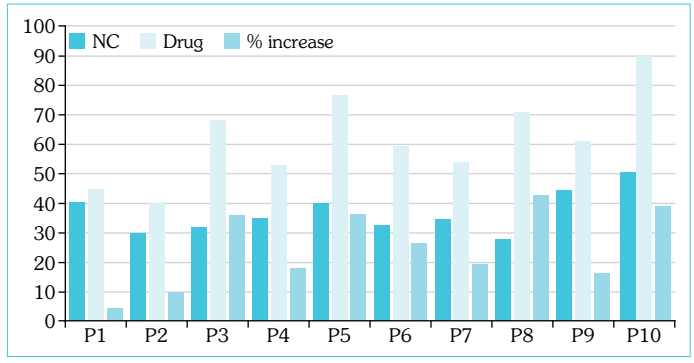

Figure 6. Displayed increase in CD63+ Cells in the 1 mg drug dilution compared to NC
P: Patient; NC: Negative control

DISCUSSION

The application of BAT to patients who developed immediate drug hypersensitivity reactions such as urticaria and/or angioedema against rocuronium resulted in a significant 28.6% increase in CD63 expression at a drug concentration of 0.1 mg/ml when compared to the negative control, and all patients in the study were found to be positive. A mean increase of 33% was demonstrated in the 1 mg/ml drug concentrations in CD203 expression, and 80% of the patients were

found to be positive. These results, which in the present study were in addition to the appropriate rocuronium concentrations to be used in the BAT test for diagnostic purposes being ascertained, suggest that rocuronium BAT applications in immediate drug hypersensitivity reactions to rocuronium with skin and/or mucosa findings can be considered a safe in vitro test method that can contribute to the diagnosis.

The NMBA drugs used during general anesthesia are known to be linked to anaphylaxis, and are associated with high morbidity and mortality in the perioperative period (12). No correlation has been identified to date between the skin tests and medical history of patients, and provocation tests using these drugs cannot be conducted, and so there is a need for additional diagnostic approaches in the event of immediate drug hypersensitivity reactions to NMBAs (13, 14). Having emerged as a promising alternative approach to the in vitro diagnosis of IgE-mediated reactions (15), BAT, which is based on the detection of allergen-origin CD63 expression or the increased regulation of CD203c on the basophil membrane. In the present study we assess the contribution of BAT to the diagnosis of immediate drug hypersensitivity reactions to rocuronium, as a frequently used NNMB agent in the study hospital.

BAT has been shown to aid in the diagnosis of immediate drug hypersensitivity reactions to various drugs, including muscle relaxants, beta-lactams and nonsteroidal anti-inflammatory drugs (5, 15–17). Eight patients with a history of perioperative anaphylaxis were evaluated and found to be positive against rocuronium by the skin test; in addition, 14 patients had tolerated rocuronium and had negative skin tests, with the sensitivity and specificity of BAT shown to be 91.7% and 100%, respectively (15). In another study, for which the authors stated that the sensitivity of the test for each agent could not be determined since the number of patients was inadequate, but who reported a general performance of BAT of 68% sensitivity and 100% specificity (18), 22 patients who developed immune hypersensitivity reactions to intra-anesthetic NMBAs were compared with 34 surgical patient controls, and BAT recorded different sensitivity rates for different NMBAs. In yet another study that supports these results, the sensitivity of BAT for NMBAs was reported as 80% and the specificity was 91.7% (19). Abuaf et al. (20) performed a study in which 48 patients with a history of anaphylaxis against NMBA were included. In the group of 28 patients known to have definite NMBA-related anaphylaxis (characterized by tachycardia, hypotension, urticaria or angioedema), and although BAT was less sensitive than skin testing, showed that BAT is more specific than skin testing and can be useful in investigating perioperative anaphylactic reactions. The authors reported a sensitivity and specificity of BAT of 64% and 93%, respectively. Li et al. (21), in their study of 120 patients with a history of NMBA administration, reported a sensitivity and specificity of BAT of 77% and 76%, respectively, in their study involving the use of skin tests with an NMBA panel (rocuronium, vecuronium, pancuronium and suxamethonium). In general, most studies to date have reported the sensitivity of BAT to NMBAs to be 36%–92%, and a specificity of 93%–100% according to the selected threshold (12, 15, 20, 22).

CD63% expression was positive at all doses of 0.01 and 0.1 mg, while positivity was 90% in the 1 mg drug dose in the present study. The highest mean CD63% difference was found with the 0.1 mg/ml dose, with an increase of 28.7% when compared to the negative control. Consistent with the present study, the optimum CD63 expression was found with the 0.1 mg/ml drug dilution in studies performed using a CD63 surface marker (15, 19, 21).

Positivity was identified in 70% of patients with 0.01 and 0.1 mg drug dilutions for CD203% expression, while positivity was found in 80% of patients with a 1 mg drug dose. The highest mean CD203% difference was found in the 1 mg/ml dose, with an increase of 32.9% over the negative control (21, 23).

One of the main limitations of the present study is the small number of cases analyzed. That said, as a very well selected patient cohort with an objective immediate drug hypersensitivity reaction was finally included in the study, patients with a history of immediate drug hypersensitivity reactions, such as urticaria and/or angioedema, developing in a very short time, were included in the study. Another limitation of the study is that the diagnoses of immediate drug hypersensitivity reactions to rocuronium in the study were taken from the patient history. Skin tests with recuronium, other drugs used perioperatively, and latex were not performed for two reasons. First, most of the patients refused to be performed in-vivo tests. The other is that the anesthesiologist stated that urticaria and/or angioedema developed immediately after applying rocuronium, and recuronium was thought to be the responsible agent for the reactions according to the history. Even if skin tests were performed with this NMBA and this test result is negative, it could not be performed due to ethical reasons although provocation with rocuronium is the gold standard diagnostic method, this as rocuronium sensitivity would not be excluded because the history was very typical, and therefore typical history was accepted as the gold standard diagnosis. In fact, BAT positivity with recuronium also supported this situation.

Finally, the study included no control group, although calculation of the sensitivity and specificity of in vitro BAT tests to rocuronium fell outside the scope of the present study.

CONCLUSION

In conclusion, the potential contributions of BAT to the diagnosis of immediate drug hypersensitivity reactions to rocuronium have been investigated in the present study. This study showed that BAT could contribute to the diagnosis when applied to patients who were administered more than one drug simultaneously with rocuronium in the perioperative period, and who experienced hypersensitivity reactions with skin/mucosa symptoms.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 03.03.2017, number: 2017/145).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – FD, İY; Design – İY, FD, MYK, DGC; Supervision – İY, FD; Resource – FD; Materials – FD, DGC, TR, SÖ; Data Collection and/or Processing – FD, DGC, TR, SÖ, MYK; Analysis and/or Interpretation – İY, FD, MYK, TR, SÖ; Literature Search – FD, İY; Writing – FD, İY; Critical Reviews – FD, İY.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study has been supported by the Scientific Research Unit of the Erciyes University with project number TYL-2018-8337.

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