

Reply to “Analyzing environmental control studies by the achieved decrease in exposure”



To the Editor:

I appreciate Miller's comments¹ and I agree with his conclusions. I would use his letter to suggest a few extensions of the conclusions in my editorial.² First, any trial of clinical effects of allergen avoidance measures should include measures of allergen exposure; this is the only way that we will understand the pathways to symptom change in treatment and control groups, and be able to test the conclusions in the Grant paper.³

Second, as Grant did, future trials should include the sort of analysis in the design as a secondary analysis, but one that is planned *a priori*.

I agree with Miller that the available meta-analysis was not an appropriate test of clinical trial outcomes. But any clinical trial outcome is strengthened by confirmation in other trials, and a meta-analysis is the most accepted way to do this; hopefully, future analyses will include more appropriate data. Colloff's book⁴ presents a confirmation of sorts but used different methods that make it difficult to merge with the analysis in the paper by Grant et al. It seems to me that the simplest route to test the conclusions would be to analyze datasets from other published allergen avoidance trials⁵ using the methods in the Grant paper. Given the quality of the trials and the availability of complete databases, such a test would be a lot easier than conducting a new trial. Again, confirmation of their findings is important before they are accepted.

Finally, we need to re-examine the populations in allergen avoidance trials—what distinguishes those who adapted control measures from those who did not? If we can better understand these differences, it will inform our strategies for future trials.

Peyton A. Eggleston, MD

Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md.

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Corresponding author: Peyton A. Eggleston, MD, Johns Hopkins Hospital, 600 N. Wolfe Street, CMSC 11-103, Baltimore, MD 21287. E-mail: pegglest@jhmi.edu.

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Does sugammadex have multiple mechanisms for causing anaphylaxis?



To the Editor:

We read with great interest and were very impressed by the report regarding sugammadex-induced anaphylaxis by Ebo et al.¹ In their patient who developed anaphylaxis after the administration of sugammadex, they showed that sugammadex acted as an antigen only after forming a complex with rocuronium. Although similar cases have been previously reported,^{2,3} their detailed skin tests and basophil activation tests (BATs) enabled them to investigate the immune mechanisms in detail.

Skin tests in their patient did not show positive responses to either sugammadex or rocuronium alone, but the results were positive with the sugammadex-rocuronium complex (S-R-Cx). Next, wortmannin, a selective inhibitor of IgE-dependent pathways in basophil activation, suppressed basophil activation by S-R-Cx, suggesting that this reaction is IgE dependent. Furthermore, because replacement of the complex host, namely sugammadex, by other cyclodextrins, including 2-hydroxypropyl- β -cyclodextrin and 2-hydroxypropyl- γ -cyclodextrin, did not activate basophils, they argued that the reaction was likely to be specific for sugammadex. Replacing the complex guest with other neuromuscular-blocking agents still resulted in a positive response. Although these are important findings and their thoughtful experimental methods should be praised, we believe that the mechanisms underlying sugammadex-induced anaphylaxis are not necessarily limited to those suggested by Ebo et al.¹

We recently conducted skin tests for a patient suspected of anaphylaxis due to sugammadex. Written informed consent for publishing this report was obtained from the patient. A 21-year-old woman underwent arthroscopic knee surgery. Although the procedure was performed uneventfully under general anesthesia, hypotension and extensive erythema appeared after bolus injection of 100 mg sugammadex. Suspecting a possible allergic reaction to sugammadex, we administered hydrocortisone, antihistamines, and a large volume of crystalloid solution. Since her hemodynamic condition stabilized, she was transferred to the intensive care unit. She was discharged 4 days after the event. One and a half months after the event, we performed skin tests with all suspected drugs used for general anesthesia, which demonstrated positive responses to both sugammadex and S-R-Cx (Table I).

To further explore the antigen, we conducted a second skin test 1 month after the first skin test (Table I). The second test suggested that the antigenic site was not the cyclodextrin ring of the main structure of sugammadex, and that it was not essential to form a complex with rocuronium.

Furthermore, we have previously shown by BATs that sugammadex alone can activate basophils in patients who show positive reactions to sugammadex in skin tests.^{5,6} Because BATs assess the effect of rocuronium and sugammadex on basophil activation separately, this evidence supports our hypothesis.

Similar to the solid results of Ebo et al, previous reports have also suggested that sugammadex exhibits antigenicity only after

TABLE I. Results of the first and second intradermal tests

Drug	Maximum concentration (mg/mL)	Maximum concentration (mM)	Judgment	Dilution	Wheal (mm)	Flare (mm)
First tests						
Histamine	0.01	NA	+	1:1	15	25
Saline	NA	NA	–	1:1		
Propofol	1	NA	–	1:1		
Remifentanyl	0.005	NA	–	1:1		
Fentanyl	0.005	NA	–	1:1		
Rocuronium	0.05	NA	–	1:1		
Sugammadex A	10	4.59	+	1:100	7	8
S-R-Cx	NA	*	+	1:100	6	7
Latex	NA	NA	–	1:1		
Chlorhexidine	0.002	NA	–	1:1		
Second tests						
Histamine	0.01	NA	+	1:1	20	25
Saline	NA	NA	–	1:1		
Sugammadex A	10	4.59	+	1:10	10	18
Sugammadex B	10	4.59	+	1:10	11	13
S-R-Cx	NA	*	+	1:10	6	8
α-Cyclodextrin	NA	4.59	–	1:1		
β-Cyclodextrin	NA	4.59	–	1:1		
γ-Cyclodextrin	NA	4.59	–	1:1		

NA, Not applicable; SPT, skin prick test; *α*-cyclodextrin, 2-hydroxypropyl-*α*-cyclodextrin; *β*-cyclodextrin, 2-hydroxypropyl-*β*-cyclodextrin; *γ*-cyclodextrin, 2-hydroxypropyl-*γ*-cyclodextrin.

In the second inspection, we did not perform SPTs, because all culprit drugs showed negative results in the first SPTs. We prepared solutions with 100-fold dilution, 10-fold dilution, and maximum concentration, and administered them in order from the lowest to highest concentration. “Dilution” in the table indicates the degree of dilution of the test solution when the skin reaction was positive, or the highest concentration of drug that did not produce a positive result. Intradermal test reactions were deemed positive when the diameter of the reactionary erythematous wheal was equal to at least twice that of the postinjection wheal after 20 minutes.⁴ In addition to sugammadex A, which is clinically used, we tested sugammadex B, which is sugammadex bulk powder without additives. Furthermore, S-R-Cx with excess rocuronium was tested.

*The maximum concentration of sugammadex and rocuronium in S-R-Cx was 1.53 mM and 1.64 mM, respectively. S-R-Cx contained sugammadex A.

forming a complex with rocuronium.^{2,3} Although we agree that this is a potential candidate mechanism of sugammadex anaphylaxis, there are certainly cases where it is not essential for sugammadex to form a complex with rocuronium to exert its antigenicity. Therefore, we hypothesized that there are multiple mechanisms of sugammadex-induced anaphylaxis, which will need to be clarified in the future.

Masaki Orihara, MD, PhD^a

Kazuhiro Nagumo, MD^a

Tomonori Takazawa, MD, PhD^b

^aDepartment of Anesthesiology, Gunma University Graduate School of Medicine, Gunma, Japan

^bIntensive Care Unit, Gunma University Hospital, Gunma, Japan.

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Corresponding author: Tomonori Takazawa, MD, PhD, Intensive Care Unit, Gunma University Hospital, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. E-mail: takazawt@gunma-u.ac.jp.

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To the Editor:

We welcome the appreciation by Orihara et al¹ of our efforts to elucidate the molecular basis of allergic recognition of the sugammadex-rocuronium inclusion complex (S-R-Cx).² In our particular case, and in accord with earlier predictions,³ the S-R-Cx was shown to be allergenic and to trigger IgE/FcεRI-dependent anaphylaxis due to a shape alteration involving the thio (carboxyethyl)sodium side chains attached at the primary rim of the host sugammadex molecule, creating a new allergenic determinant. Because these changes appeared not specific for the guest rocuronium, the use of sugammadex as a selective