

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.

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Reply to “Does sugammadex have multiple mechanisms for causing anaphylaxis?”



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

relaxant-binding agent for other steroidal neuromuscular-blocking agents is precluded in this case.

In their correspondence, Orihara et al¹ state that “the mechanisms underlying sugammadex-induced anaphylaxis are not necessarily limited to those suggested by Ebo et al²” and their title suggests sugammadex to have multiple mechanisms for anaphylaxis. However, our S-R-Cx article² does not claim or infer that the mechanisms underlying sugammadex-induced anaphylaxis are restricted to IgE-mediated reactions to allergenic changes at the sugammadex primary rim and the authors presumably mean anaphylaxis to sugammadex can occur via multiple mechanisms that can culminate in effector cell degranulation and perioperative anaphylaxis.⁴ Consistent with the prediction of “the possible allergenic properties of the cyclodextrin host itself and of the guest-host compound molecule,”³ numerous reports have already shown that it is not essential for sugammadex to form a complex with rocuronium to exert its allergenicity (for review, see Baldo⁵).

In an attempt to disentangle the molecular basis of recognition of sugammadex in their patient, Orihara et al¹ performed a second set of skin test experiments with sugammadex, S-R-Cx, and different other cyclodextrins. Because γ -cyclodextrin proved skin test negative and sugammadex positive, the authors conclude there are “multiple mechanisms of sugammadex-induced anaphylaxis.” However, in our opinion, skin test reactivity to sugammadex and not to γ -cyclodextrin is not a proof for an alternative pathomechanism as indicated in the title. The differences in skin test responsiveness between sugammadex and γ -cyclodextrin in this particular patient again suggest involvement of the added thio (carboxyethyl)sodium groups that convert γ -cyclodextrin to sugammadex. Additional *ex vivo* basophil activation experiments with and without the phosphoinositide 3-kinase inhibitor wortmannin should help to clarify whether the reaction in this patient is IgE-mediated, because positive skin test responses might result from alternative mechanisms. In patients suffering from perioperative anaphylaxis in close temporal relationship to administration of sugammadex who demonstrate negative test results for the reversal drug, it is mandatory to offer complementary tests with the S-R-Cx.

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