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LETTER TO THE EDITOR

Can sugammadex encapsulation eliminate the antigenic activity of aminosteroidal neuromuscular blocking agent?

Takashi Kawano · Masataka Yokoyama

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To the Editor:

Anaphylaxis is one of the most serious adverse events caused by neuromuscular blocking agents (NMBAs) [1]. In the epidemiological surveys conducted in Europe, it was found that NMBAs are responsible for approximately 50–70% of the anaphylactic reactions that occur during anesthesia [1, 2]. The quaternary ammonium (QA) ions, which are essential for the neuromuscular-blocking effects of NMBAs, have been suggested to be the allergenic epitope of NMBAs [1]. Therefore, all NMBAs may cause anaphylaxis, and allergic cross-reactivity between NMBAs has been reported [1, 2].

Sugammadex can bind to aminosteroidal NMBAs (e.g., rocuronium and vecuronium) via chemical encapsulation and cause reversal of the neuromuscular blockade. Recently, McDonnell et al. [3] reported a case in which rapid improvement of rocuronium-induced anaphylaxis was observed after sugammadex administration. Although this case indicates that sugammadex may be a novel therapeutic agent for NMBA-induced anaphylaxis, the underlying mechanism(s) of its therapeutic effects remains unknown. The lack of a suitable animal model makes it difficult to study the effects of sugammadex therapy. However, one possible mechanism is that the QA epitopes on NMBA molecules are eliminated from circulation by sugammadex encapsulation [4].

To confirm this hypothesis, we conducted an in vitro experiment using specific reagent strips as QA indicator (Merkoquant®117920; Merck KGaA, Germany) to observe whether NMBA QA epitopes were encapsulated by sugammadex. QA compounds react with the indicator, resulting in a change in color of the test strips from yellow to green. These test strips showed positive results (green) for all tested NMBAs such as rocuronium, vecuronium, and succinylcholine, but showed a negative result (yellow) for sugammadex alone (Fig. 1). However, the QA reaction of rocuronium (50 μg/ml) and vecuronium (50 μg/ml) was diminished when they were premixed with sugammadex (≥200 μg/ml; response ratio 4:1). On the other hand, even the highest test concentration (400 μg/ml) of sugammadex had no effect on QA response of succinylcholine (50 μg/ml) (Fig. 1). As sugammadex has no binding affinity for succinylcholine, we assume that the interaction of sugammadex with the QA epitopes of aminosteroidal NMBAs is associated with the formation of chemical encapsulation.

Our results suggest that a high dose of sugammadex can rapidly hide the QA epitopes on the surface of circulating aminosteroidal NMBAs. This may subsequently prevent QA epitopes of NMBAs binding to immunoglobulin E, thus interrupting the anaphylactic reaction and prevent mediator release. In consistent with our findings, Leysen et al. [5] reported that sugammadex prevented in vitro basophil activation induced by rocuronium in three patients with established rocuronium allergy. However, QA epitopes are reported to be the most important, but not only, allergenic determinant of NMBAs [1, 2]. Furthermore, Leysen et al. [5] demonstrated that sugammadex failed to halt ongoing rocuronium-induced basophil activation. Therefore, it still remains unknown whether sugammadex

T. Kawano (✉) · M. Yokoyama
Department of Anesthesiology and Critical Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan
e-mail: takashika@kochi-u.ac.jp

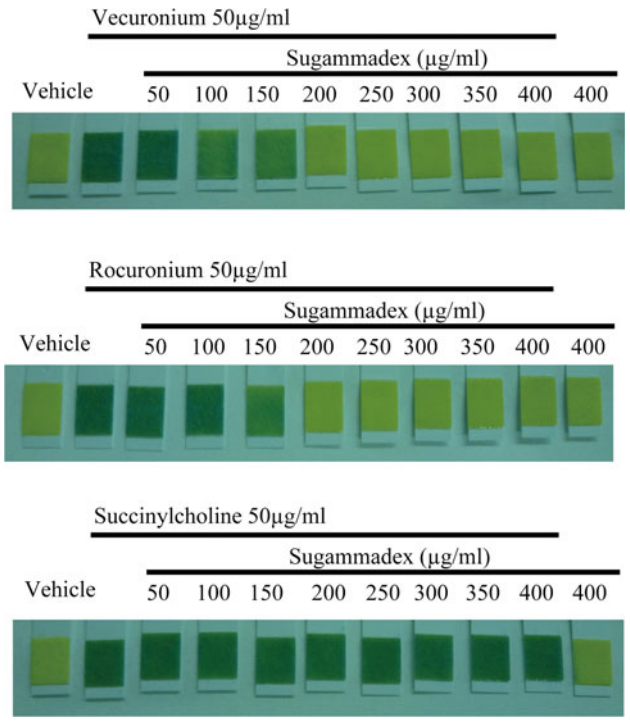

Fig. 1 Semiquantitative measurement of quaternary ammonium (QA) groups in rocuronium, vecuronium, and succinylcholine by visual detection of a specific indicator. Vehicle (distilled water) and sugammadex alone showed no reaction. All experiments were performed in triplicate, and the same pattern of reactions was observed

can entirely eliminate the antigenic activity of aminosteroidal NMBAs and mitigate NMBA-induced anaphylaxis in the clinical setting.

In conclusion, encapsulation of aminosteroidal NMBAs by sugammadex results in rapid elimination of QA epitopes from circulation. Our finding warrants further investigation of sugammadex as a novel therapeutic agent for treating aminosteroidal-NMBA-induced anaphylaxis.

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