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Title: Evaluation of Preoperative Risk Factors for Sugammadex-Induced Anaphylaxis:
Analysis of the Japanese Adverse Drug Event Report Database

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Sugammadex is a synthetic cyclodextrin derivative that reverses the effect of neuromuscular blocking agents such as rocuronium and vecuronium.¹ Sugammadex allows rapid and reliable reversal of neuromuscular block, but one of the adverse events associated with this agent is anaphylaxis. Although the dose of sugammadex is a known risk factor for sugammadex-induced anaphylaxis,^{2,3} it is unclear if there are any preoperative risk factors. Obtaining preoperative information and assessing the risk of sugammadex-induced anaphylaxis may help avoid serious adverse events. Herein, we investigated preoperative factors associated with reporting of anaphylaxis with sugammadex compared with other adverse events using the Japanese Adverse Drug Event Report (JADER) database. Institutional review board approval was not required because of the anonymity of the patient information in this database.

Data recorded up until May 2021 were downloaded from the Pharmaceuticals and Medical Devices Agency website (<http://www.pmda.go.jp/>) on October 3, 2021. Sugammadex or neostigmine users were identified. Neostigmine was defined as the comparator because it was used in recovery from anesthesia before the advent of sugammadex.⁴ The cut-off dose for sugammadex was set at 4 mg/kg because a dose ≥ 4 mg/kg is generally used.⁵ Use of an angiotensin-converting enzyme inhibitor or beta-blocker was also included because these drugs have been reported to increase the risk of anaphylaxis.⁶ Details of these drugs are shown in Supplemental Table S1. Anaphylaxis was defined as “anaphylactic shock,” or “anaphylactic reaction.” Exclusion criteria are shown in Supplemental Figure S1. All analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Disproportionality for anaphylaxis was detected in sugammadex users only (reporting odds ratio 16.6, 95% confidence interval [CI] 13.9–19.7, $P < 0.01$). Multivariate

logistic analysis showed that the reports of anaphylaxis were significantly more common in the presence of drinking alcohol (odds ratio [OR] 3.34, 95% CI 1.36–8.19, $P < 0.01$) and food allergy (OR 5.55, 95% CI 1.18–26.2, $P = 0.03$) (Table 1) and were significantly less common at a sugammadex dose ≥ 4 mg/kg (OR 0.54, 95% CI 0.34–0.87, $P = 0.01$).

This suggests that reports of anaphylaxis with sugammadex may be associated with drinking alcohol and food allergy. Drinking alcohol has been reported to be associated with an elevated immunoglobulin E level.⁷ The gamma-cyclodextrin structure of sugammadex may trigger an allergic response in patients with food allergies, and these gamma-dextrin structure may be a risk factor for anaphylaxis.² However, the detailed mechanism of sugammadex-induced anaphylaxis has not yet been clarified. The risk of anaphylaxis was low at a sugammadex dose ≥ 4 mg/kg; however, it has been reported that hypersensitivity is more likely at a dose of 16 mg/kg than at 4 mg/kg.³ Therefore, there may be little risk of anaphylaxis at a dose of around 4 mg/kg. The main limitation of this study is that the JADER database might be prone to reporting bias, which could explain the high frequency of anaphylaxis. Overall, however, the evidence of this association should be assessed further in future studies.

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Table 1 Multivariate logistic analysis of potential risk factors by reported anaphylaxis compared to other adverse events in patients using sugammadex

	Anaphylaxis / Total, n (%)	Odds ratio (95% CI)		P-value*
		Crude	Adjusted	
Female sex	135/274 (49.3)	1 [Reference]	1 [Reference]	0.26
Male sex	120/273 (44.0)	0.81 (0.58–1.13)	0.81 (0.57–1.16)	
Age < 60 years	117/229 (51.1)	1 [Reference]	1 [Reference]	0.38
Age ≥ 60 years	138/318 (43.4)	0.73 (0.52–1.03)	0.85 (0.59–1.22)	
Sugammadex dose < 4 mg/kg	220/450 (48.9)	1 [Reference]	1 [Reference]	0.01
Sugammadex dose ≥ 4 mg/kg	35/97 (36.1)	0.59 (0.38–0.93)	0.54 (0.34–0.87)	
Without drinking alcohol	236/521 (45.3)	1 [Reference]	1 [Reference]	<0.01
With drinking alcohol	19/26 (73.1)	3.28 (1.35–7.93)	3.34 (1.36–8.19)	
Without asthma	246/531 (46.3)	1 [Reference]	1 [Reference]	0.70
With asthma	9/16 (56.3)	1.49 (0.55–4.06)	1.22 (0.43–3.45)	
Without atopic disease	253/544 (4.5)	1 [Reference]	1 [Reference]	0.92
With atopic disease	2/3 (66.7)	2.3 (0.21–25.5)	1.15 (0.09–15.3)	
Without food allergy	245/535 (45.8)	1 [Reference]	1 [Reference]	0.03
With food allergy	10/12 (83.3)	5.92 (1.28–27.3)	5.55 (1.18–26.2)	
Without mastocytosis	0/547 (0)	NA	NA	NA
With mastocytosis	0/0			
Without ACE inhibitor	254/539 (47.1)	1 [Reference]	1 [Reference]	0.07
With ACE inhibitor	1/8 (12.5)	0.16 (0.02–1.31)	0.12 (0.01–1.19)	
Without beta-blockers	247/528 (46.8)	1 [Reference]	1 [Reference]	0.29
With beta-blockers	8/19 (42.1)	0.83 (0.33–2.09)	1.82 (0.60–5.46)	
Use of vecuronium	2/3 (66.7)	1 [Reference]	1 [Reference]	0.39
Use of rocuronium	253/544 (46.5)	0.44 (0.04–4.82)	0.34 (0.03–3.92)	

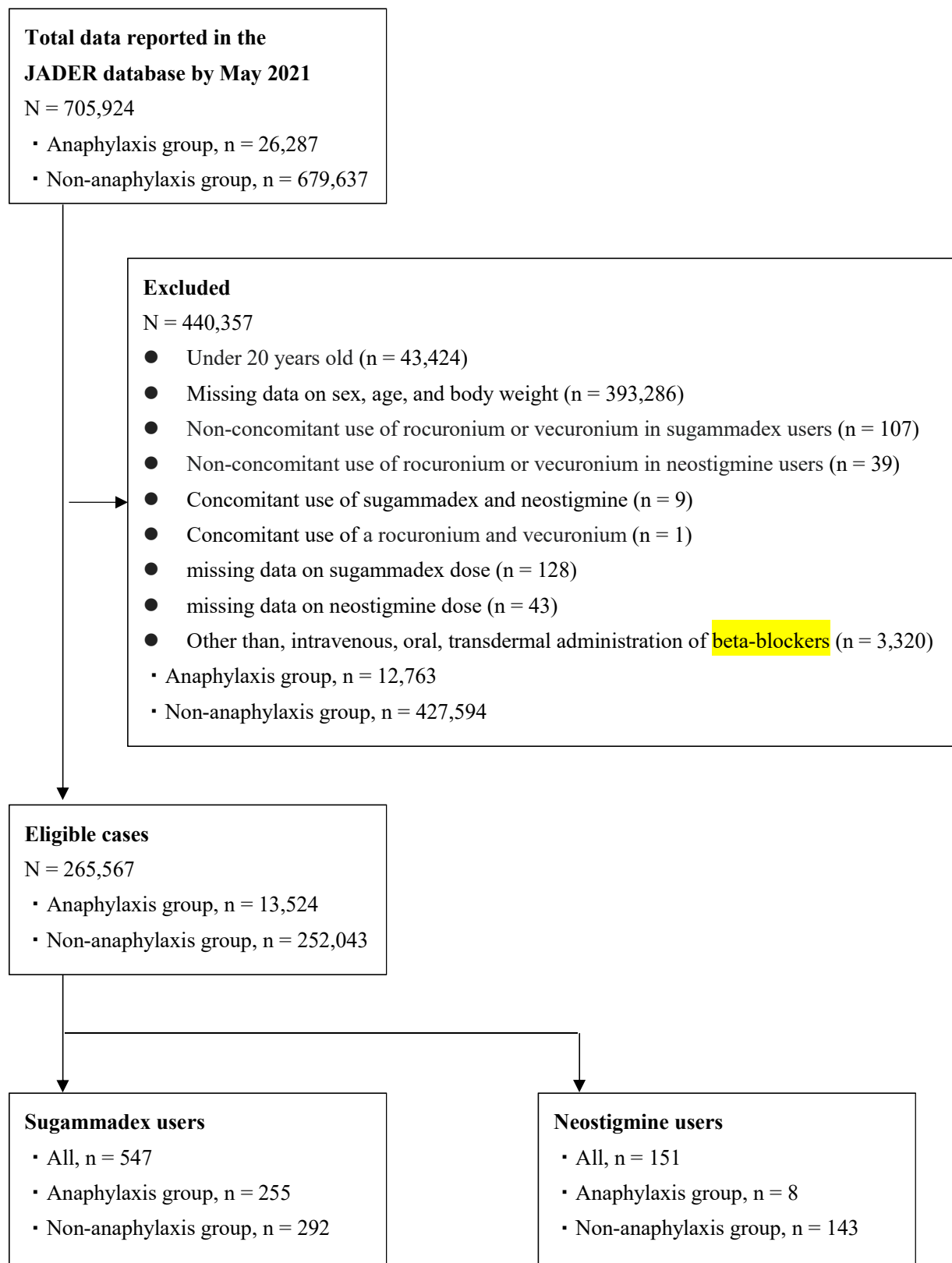
*Multivariate logistic analysis.

A P-value < 0.05 was considered statistically significant.

Modeling was based on complete case analysis.

ACE, angiotensin-converting enzyme.

NA, not applicable



Supplemental Figure S1 Flow chart of patients in this study
JADER, Japanese Adverse Drug Event Report

Supplemental Table S1 List of angiotensin-converting enzyme inhibitors and beta-blockers

Classification	Drugs
Angiotensin-converting enzyme inhibitors	Benazepril
	Captopril
	Cilazapril
	Enalapri
	Imidapril
	Lisinopril
	Perindopril
	Quinapril
	Temocapril
	Trandolapril.
Beta-blockers	Acebutolol
	Atenolol
	Betaxolol
	Bisoprolol
	Carteolol
	Celiprolol
	Metoprolol
	Nadolol
	Pindolol
	Propranolol