

ORIGINAL ARTICLE

Intraoperative anaphylaxis to neuromuscular blocking agents: the incidence over 9 years at two tertiary hospitals in South Korea

A retrospective observational study

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BACKGROUND Intraoperative anaphylaxis to neuromuscular blocking agents (NMBAs) is a rare event that is unpredictable and potentially life threatening. Most of the previous reports on such intraoperative anaphylaxis used market share surveys or self-reported data to estimate the incidence.

OBJECTIVE To determine the incidences of intraoperative anaphylaxis to NMBAs using electronic medical records.

DESIGN A retrospective observational study.

SETTING Two tertiary hospitals in South Korea.

PATIENTS This study involved patients exposed to NMBAs during anaesthesia between 1 January 2005 and 31 May 2014. Nineteen episodes were deemed to be intraoperative anaphylaxis to NMBAs.

MAIN OUTCOME MEASURES We calculated the incidences of intraoperative anaphylaxis to NMBAs. Exposure to the agents was determined from intraoperative records maintained in an electronic medical recording system. An

anaphylactic reaction was determined from both clinical signs and the results of skin tests.

RESULTS Over 9 years, 729 429 patients were exposed to NMBA, the most frequently used being rocuronium [425 047 (58.3%)] and vecuronium [274 801 (37.7%)]. The overall incidence of intraoperative anaphylaxis was 2.6 per 100 000 (19 cases), and was higher with rocuronium (16 cases, 3.8 per 100 000) than with vecuronium (two cases, 0.7 cases per 100 000), $P=0.014$. Comparing the first 3 years with the last 6 years, the incidence of intraoperative rocuronium anaphylaxis appeared to increase 1.4-fold ($P=0.006$).

CONCLUSION Among commonly used NMBAs, rocuronium appears to have the highest incidence of anaphylaxis. Our findings suggest that future prospective investigation for NMBA-induced anaphylaxis should use internationally agreed skin test protocols.

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Introduction

Anaphylaxis is defined as a severe, life-threatening, systemic hypersensitivity reaction.^{1,2} Perioperative anaphylaxis has been reported to occur in approximately one in 10 000 to 20 000 anaesthetics.^{3–5} A neuromuscular blocking agent (NMBA) is one of the most frequently implicated causes of intraoperative anaphylaxis,^{2,5–8} with an estimated incidence of one case in 5000 to 6000 anaesthetics.^{4,5,7} Recently reported incidences of anaphylaxis

(per 100 000 patient exposures) to specific NMBAs are 8.0 for rocuronium and 2.8 for vecuronium.⁹ Concerns about the higher incidence of rocuronium-induced anaphylaxis have developed since its introduction.^{2,10–12}

However, in most previous reports, the incidences of NMBA anaphylaxis during anaesthesia were based on surrogates for patient exposure (e.g., market share surveys

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or drug ampoule sales data),^{8,9,13–15} or physician reporting cases to specific centres.^{7,14,15} Moreover, most reports were not conducted on an Asian population.^{7,9,13–15}

An electronic medical records (EMRs) recording system was introduced into our two hospitals in 2005 and we analysed the incidence of intraoperative NMBA anaphylaxis over a 9-year period by using data held in these records.

Methods

The present retrospective study involved patients exposed to NMBAs during anaesthesia between 1 January 2005 and 31 May 2014, at two tertiary hospitals in South Korea (Seoul National University Hospital and Samsung Medical Centre). Ethical approval for this study was provided by the Institutional Review Board of Seoul National University College of Medicine/Seoul National University Hospital (Chairperson Dr Jae-Seung Paick; protocol N° 1303-072-474; date of approval, 18 June 2014) and Samsung Medical Centre Institutional Review Board (Chairperson Dr Suk-Koo Lee; protocol N° 2013-08-033; date of approval, 14 August 2013), Seoul, South Korea. The need for informed consent was waived because only a retrospective review of medical records was performed, with no intervention. Data can be retrieved from the EMR systems of these two hospitals after specifically authorised approval by the ethical committee.

Exposure

Exposure to NMBAs during anaesthesia was determined from the electronic record of intraoperative medication orders, signed by anaesthetists attending the operations. We requested the medical information centres of the two hospitals to search the EMR database, between 1 January 2005 and 31 May 2014, for intraoperative medication orders which included any of the following locally available NMBAs: rocuronium, vecuronium, succinylcholine, atracurium, cisatracurium. If a patient underwent two or more operations during the study period, each NMBA administration was considered to be a separate exposure to that NMBA. If a patient was given more than one ampoule of an NMBA during anaesthesia for any reason, such as prolonged surgery time or a high BMI, exposure to that NMBA was only counted once. The data obtained were classified by the NMBA administered and the year of use. The annual and total exposures to individual NMBAs over 9 years were determined.

Reactors

Patients who may have experienced a perioperative anaphylactic event with a NMBA were identified by a separate search of the two EMR systems, and a list of patients who had undergone investigative skin tests during the study period, using any of the available NMBAs, was produced. The results of the skin tests were included in this list. We then reviewed the

electronically recorded medical and anaesthetic records of these patients to identify if an intraoperative anaphylactic event with a NMBA had occurred.

Anaphylactic reactions were evaluated by extracting the results of the allergy skin tests performed with any of the five available NMBAs. In the two hospitals included in this study, there were no written protocols or specific criteria for evaluation of patients suspected of having an adverse drug reaction or an anaphylactic event during anaesthesia. The physicians in charge referred the patients to the allergy department for further evaluation, mainly based on the clinical history: timing, clinical signs of adverse reactions which were possibly drug related, such as urticaria/angioedema, bronchospasm or cardiovascular collapse shortly after administration of the NMBA.

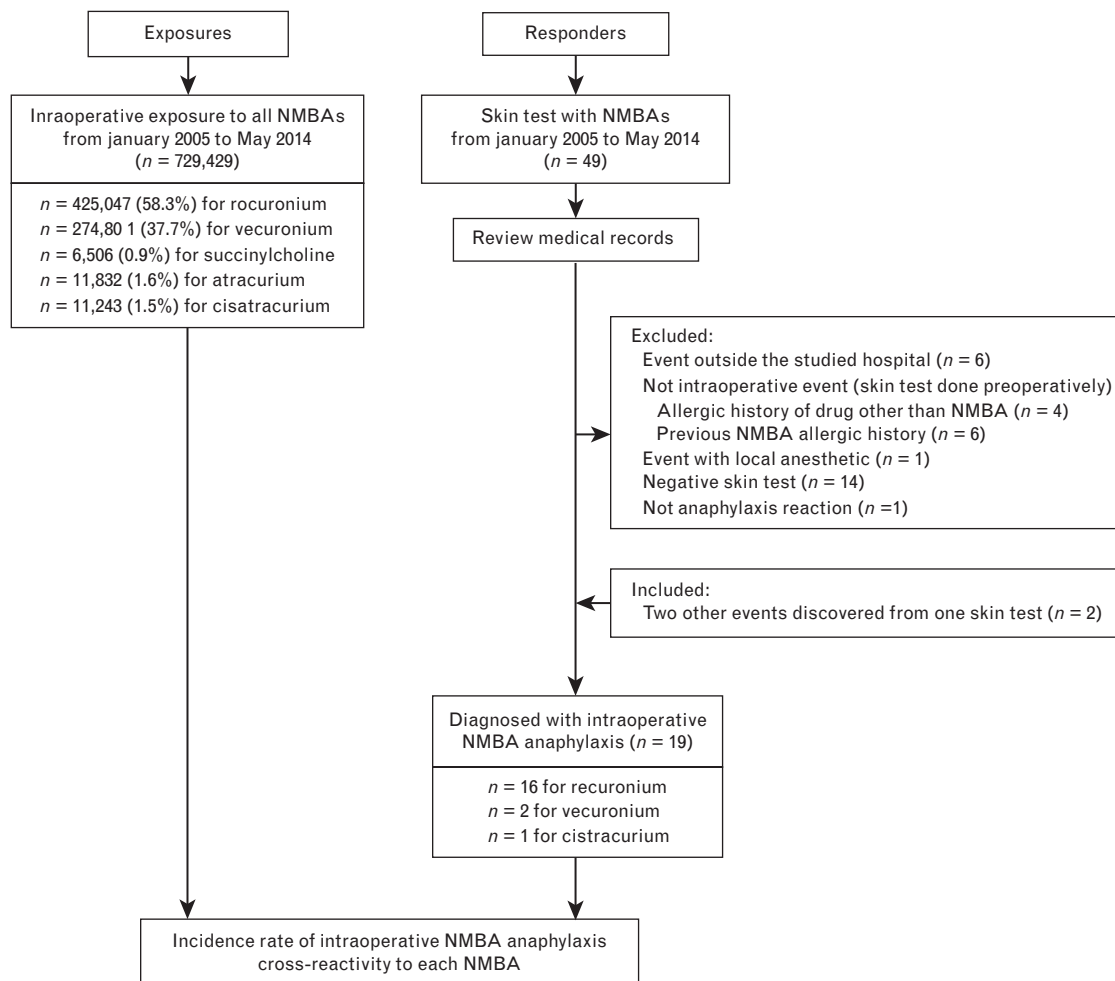
An anaphylactic reaction was assessed based on clinical guidelines^{2,16–18} and the criteria used in a previous study.⁹ First an appropriate time relationship between drug administration and the clinical features of anaphylaxis was required; second, the patient was required to have a positive skin test for the NMBA in question; third, the patient had to have a negative skin test for all other agents used before the reaction (including other anaesthetics, opioids, antibiotics, colloids and antiseptics). After identifying reactors, from the EMR data we assessed their baseline characteristics, the onset of the reaction, the clinical signs and treatment and whether or not the surgical procedure was completed.

Allergy skin test and cross-reactivity assessment

Skin testing was performed to identify the likely offending agent using the international consensus protocols.¹⁹ Briefly, patients were instructed to avoid any drugs that could influence skin reactivity for at least 72 h prior to the test day. A positive control (10 mg ml⁻¹ histamine) and a negative control (0.9% normal saline) were applied. Skin tests were performed 4 to 6 weeks after the anaphylactic event.

For skin prick and intradermal tests, drug concentrations followed the institutional protocols, based on the international consensus.^{16,20–22} For skin prick tests, the test concentrations were rocuronium 10 mg ml⁻¹ (1:1 dilution factor), vecuronium 4 mg ml⁻¹ (1:1 dilution factor), succinylcholine 10 mg ml⁻¹ (1:5 dilution factor), atracurium 1 mg ml⁻¹ (1:10 dilution factor) and cisatracurium 2 mg ml⁻¹ (1:1 dilution factor). Intradermal tests were performed with serial dilutions of the agents until the previously agreed maximum nonirritating concentrations^{6,20,22} were attained: rocuronium 0.1 mg ml⁻¹ (1:100 dilution factor), vecuronium 0.4 mg ml⁻¹ (1:10 dilution factor), succinylcholine 0.1 mg ml⁻¹ (1:500 dilution factor), atracurium 0.01 mg ml⁻¹ (1:1000 dilution factor) and cisatracurium 0.02 mg ml⁻¹ (1:100 dilution factor). These concentrations followed the

Fig. 1



Flow chart. NMBA, neuromuscular blocking agent.

recommendations available during the studied period.^{16,20–22} However, later it was proposed that the intradermal test concentrations for rocuronium and vecuronium should be lowered [0.05 mg ml^{-1} (1:200 dilution factor) and 0.04 mg ml^{-1} (1:100 dilution factor)],^{23,24} and some recommend even lower concentrations.⁹ We present our skin test results based on the higher drug concentrations proposed in the original consensus^{16,20,22} but we also present results based on the lower drug concentrations ('strict' results) as proposed more recently.^{23,24}

A skin prick test was deemed positive if the agent induced a wheal of at least 3 mm in diameter and a surrounding flare reaction. An intradermal test was deemed positive if the bleb size increased more than 3 mm in diameter from the initial bleb and was accompanied by a surrounding flare reaction. All the skin responses were interpreted at 15 min.

To identify cross-reactive agents and well tolerated alternatives for the future, skin tests should include all the currently available NMBA's, as well as all the other drugs and substances used before the reactions; however, this extent of testing varied among cases. Other laboratory tests, such as serum tryptase and total immunoglobulin E (IgE) levels, were also reviewed.

Severity of the anaphylactic reaction

As previously described,^{4,16,25} the severity of intraoperative anaphylaxis was graded using a four-level degree-of-reaction scale in which higher levels represent increasing severity. Grade 1 indicates the presence of generalised cutaneous signs: erythema, and urticaria with or without angioedema. Grade 2 is associated with measurable, but not life-threatening symptoms, including cutaneous signs, hypotension, tachycardia or bronchial hyper-reactivity (cough or ventilatory impairment). Grade 3 requires the presence of severe, life-threatening symptoms,

including cardiovascular collapse, tachycardia or bradycardia, cardiac arrhythmias or bronchospasm. Grade 4 indicates cardiac or respiratory arrest.

Statistical analysis

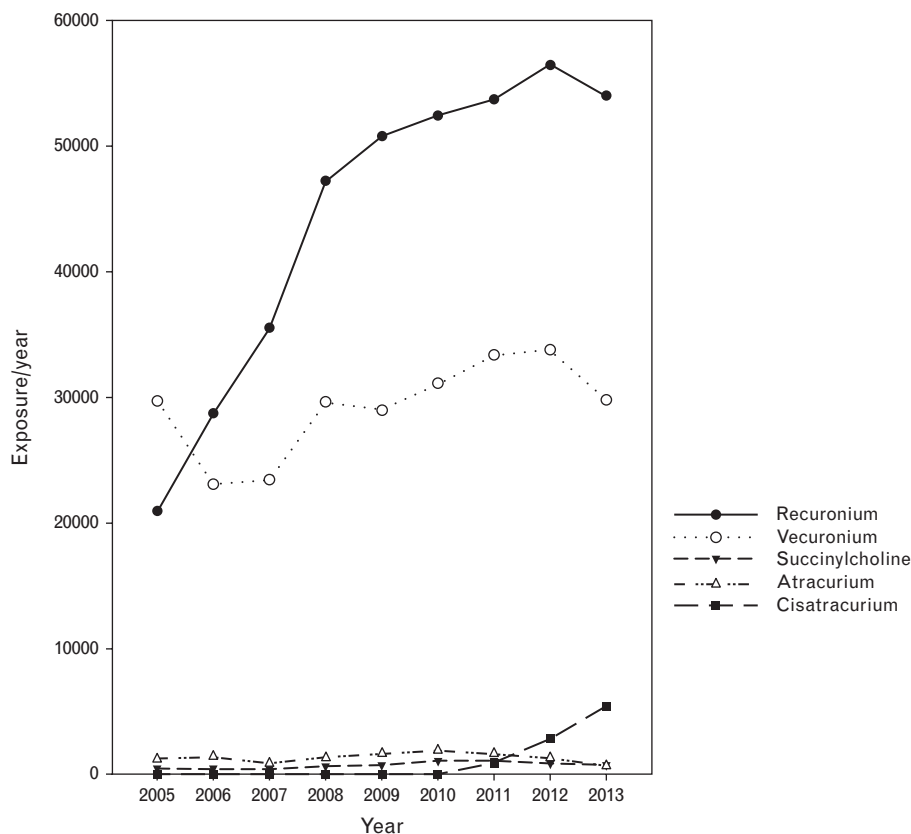
We calculated the incidence of each NMBA anaphylaxis, with 95% confidence interval (CI), according to a Poisson distribution.²⁶ Poisson regression was performed to compare the incidences of intraoperative anaphylaxis reactions to NMBAs, as well as to analyse annual trends, using SPSS software (ver. 21.0.0.0; IBM, Armonk, New York, USA). A *P* value less than 0.05 was considered to indicate statistical significance.

Results

Over the 9 years of the study, the total number of exposures to all available NMBAs during anaesthesia was 729 429 (Fig. 1). Rocuronium had the greatest use, 425 047 (58.3%), followed by vecuronium [274 801 (37.7%); Fig. 1]. In contrast to the relatively stable use of vecuronium, patient exposure to rocuronium nearly tripled during the study period (Fig. 2).

The EMR search produced a list of 49 patients who had undergone investigative skin tests with an NMBA (Fig. 1), and using the criteria outlined earlier, we reviewed the EMRs to determine whether the reactions indicated anaphylaxis to an NMBA. Nineteen episodes were suspected as being intraoperative anaphylaxis to NMBA. Of these, 16 (84.2%) were attributable to rocuronium, two (10.5%) to vecuronium, and one (5.3%) to cisatracurium (this drug had only been in use since 2011). No anaphylactic reactions to succinylcholine or atracurium were identified during the study period. Most patients (74%, 14/19) had had a previous exposure to an NMBA. More specifically, 42% (8/19) had had a previous exposure to the same NMBA (Table 1). The median age of the patients was 52 (range, 13 to 71) years, 63% of patients were female and in 42% of cases, the procedure was postponed. The mean time from administration of the suspected drug to the recognition of the clinical signs was 5 min (median 5, range 1–35 min). Of these reactions, 95% (18/19) were grade 3 in terms of severity classification, and external cardiac compression was required in one case (grade 4). Serum tryptase levels were available

Fig. 2



Number of patients exposed per year to rocuronium, vecuronium, succinylcholine, atracurium and or cisatracurium during anaesthesia between 2005 and 2013.

Table 1 Characteristics of suspected intraoperative anaphylaxis to neuromuscular blocking agents

Case No.	Year	Sex	Age (year)	NMBA responsible for the reaction	Onset ^a (min)	Skin tests with responsible NMBA		Tryptase ($\mu\text{g l}^{-1}$) [<11.0] ^b	Cross-reactivity		Previous exposure to NMBA	Other drugs tested	
						SPT	IDT		SPT	IDT		SPT	IDT
1	2009	F	48	Rocur	5	1:1+	1:200 ND 1:100 ND 1:10+	ND	Vecur 1:1– Succin 1:5– Atrac 1:10–	Vecur 1:100 ND 1:10 + Succin 1:500 + Atrac 1:1000 +	Y	Propof 1:1 – Remif 1:1 – Levof 1:1 – Lidoc 1:1 –	Propof 1:10 + Remif 1:10 + Levof 1:100 – Lidoc 1:10 –
2	2010	F	16	Rocur	5	1:10+ 1:1+	ND	ND	Vecur 1:10– 1:1 – Succin 1:10– Atrac 1:10–	Vecur 1:100 – 1:10 + Succin 1:100 – 1:10 + Atrac 1:1000 ND 1:100 +	N	Propof 1:1 – Propof 1:100 –	Propof 1:10 – 1:10 –
3	2011	F	53	Rocur	3	1:1–	1:200 ND 1:100+	ND	Vecur 1:1– Succin 1:5– Atrac 1:10– Cisatr 1:1+	Vecur 1:100 ND 1:10 + Succin 1:500 – Atrac 1:1000 +	Y	Moxif 1:1000 – Flumox 1:1 –	Moxif 1:1000 – Flumox 1:1 –
4	2011	F	38	Rocur	4	1:10+	1:1000– 1:200 ND 1:100+	ND	Vecur 1:4– Atrac 1:10–	Vecur 1:400 – 1:40 + Atrac 1:1000 – 1:100 +	Y	Propof 1:1 – Remif 1:1 –	Propof 1:10 – Remif 1:10 –
5	2011	M	62	Rocur	2	1:10+ 1:1+	ND	ND	Vecur 1:10– 1:1 – Succin 1:10– 1:1 –	Vecur 1:100 – 1:10 + Succin 1:500 ND 1:100 + 1:10 +	Y	Lidoc 1:5 – Thiop 1:10 – 1:1 –	Lidoc 1:50 – Thiop 1:100 – 1:10 –
6	2011	M	62	Rocur	5	1:10+ 1:1+	ND	ND	Vecur 1:10– 1:1 – Succin 1:10– 1:1 –	Vecur 1:100 – 1:10 + Succin 1:500 ND 1:100 + 1:10 +	Y	Lidoc 1:5 – Thiop 1:10 – 1:1 –	Lidoc 1:50 – Thiop 1:100 – 1:10 –
7	2012	F	58	Rocur	1	1:1+	ND	ND	Vecur 1:1– Succin 1:5– Atrac 1:10– Cisatr 1:1–	Vecur 1:100 – 1:10 + Succin 1:500 – Atrac 1:1000 ND 1:100 + Cisatr 1:100 +	N	Propof 1:1 – Remif 1:1 – Thiop 1:1 – Midaz 1:1 – Fentan 1:1 –	Propof 1:10 – Remif 1:10 – Thiop 1:10 – Midaz 1:10 – Fentan 1:1 –
8	2012	F	49	Rocur	10	1:1–	1:200 ND 1:100+	ND	Vecur 1:40– 1:4 – Succin 1:10– 1:1 – Atrac 1:10–	Vecur 1:400 + 1:40 + Succin 1:100 – 1:10 + Atrac 1:1000 ND 1:100 +	Y	Propof 1:10 – 1:1 – Remif 1:10 – 1:10 – Thiop 1:10 – 1:1 –	Propof 1:100 – 1:10 – Remif 1:100 – 1:10 – Thiop 1:100 – 1:10 –
9	2012	F	65	Rocur	1	1:1–	1:200 ND 1:100+	ND	Vecur 1:40– 1:4– Succin 1:10– 1:1– Atrac 1:10–	Vecur 1:400 – 1:40 + Atrac 1:1000 ND 1:100 +	Y	Propof 1:10 – 1:1 – Midaz 1:10 – 1:1 –	Propof 1:100 – 1:10 – Midaz 1:100 – 1:10 –
10	2012	M	13	Rocur	1	1:1–	1:200 ND 1:100+	ND	Vecur 1:40– 1:4–	Vecur 1:400 – 1:40 +	Y	Thiop 1:1 –	Thiop 1:100 – 1:10 –
11	2012	F	56	Rocur	5	1:1–	1:200 ND 1:100+	ND	Vecur 1:40– 1:4– Cisatr 1:10– 1:1–	Vecur 1:400 – 1:40 – Cisatr 1:100 +	Y	Thiop 1:1 –	Thiop 1:100 – 1:10 –

Table 1 (continued)

Case No.	Year	Sex	Age (year)	NMBA responsible for the reaction	Onset ^a (min)	Skin tests with responsible NMBA		Tryptase ($\mu\text{g l}^{-1}$) [<11.0] ^b	Cross-reactivity		Previous exposure to NMBA	Other drugs tested	
						SPT	IDT		SPT	IDT		SPT	IDT
12	2012	M	45	Rocur	1	1:1+	ND	ND	ND	Vecur 1:100 ND 1:10 + Cisatr 1:100 +	Y	ND	Propof 1:10 – Remif 1:10 – Fentan 1:10 –
13	2013	F	52	Rocur	2	1:1+	1:200 ND 1:100 ND 1:10+	1.8	Vecur 1:1 – Succin 1:5 – Atrac 1:10 –	Vecur 1:100 ND 1:10 + Succin 1:500 + Atrac 1:1000 +	Y	Propof 1:1 – Remif 1:1 – Levof 1:1 – Lidoc 1:1 –	Propof 1:10 + Remif 1:10 + Levof 1:100 – Lidoc 1:10 –
14	2013	F	33	Rocur	1	1:1 –	1:200 ND 1:100+	ND	Vecur 1:1 – Succin 1:5 – Cisatr 1:1 –	Vecur 1:100 ND 1:10 + Succin 1:500 – Cisatr 1:100 +	Y	Propof 1:1 – Lidoc 1:1 – Thiop 1:1 – Etomid 1:1 – Midaz 1:1 – Fentan 1:1 –	Propof 1:10 – Lidoc 1:10 – Thiop 1:10 – Etomid 1:10 – Midaz 1:10 + Fentan 1:10 –
15	2013	F	51	Rocur	35	1:1 –	1:200 ND 1:100+	6.8	Vecur 1:1 – Succin 1:5 – Cisatr 1:1 –	Vecur 1:100 ND 1:10 + Succin 1:500 – Cisatr 1:100 +	N	Propof 1:1 – Remif 1:1 –	Propof 1:10 – Remif 1:10 –
16	2014	F	28	Rocur	2	1:1+	1:200 ND 1:100+	ND	Vecur 1:1 – Succin 1:5 – Cisatr 1:1 –	Vecur 1:100 ND 1:10 + Succin 1:500 – Cisatr 1:100 +	N	Propof 1:1 – Remif 1:1 – Thiop 1:1 – Etomid 1:1 – Midaz 1:1 – Fentan 1:1 –	Propof 1:10 – Remif 1:10 – Thiop 1:10 – Etomid 1:10 – Midaz 1:10 + Fentan 1:10 –
17	2011	M	37	Vecur	10	1:1 –	1:100 ND 1:10+	ND	Rocur 1:1 – Succin 1:5 – Atrac 1:10 – Cisatr 1:1 –	Rocur 1:200 ND 1:100 + Succin 1:500 – Atrac 1:1000 ND 1:100 + Cisatr 1:100 +	Y	Propof 1:1 – Remif 1:1 – Thiop 1:1 – Midaz 1:1 – Sufent 1:1	Propof 1:10 – Remif 1:10 – Thiop 1:10 – Midaz 1:10 – Sufent 1:10 +
18	2011	M	71	Vecur	1	1:40 – 1:4 –	1:400 – 1:40+	ND	Rocur 1:10 – 1:1 – Succin 1:10 – Atrac 1:10 – Cisatr 1:10 – 1:1 –	Rocur 1:200 ND 1:100 + Succin 1:100 – Atrac 1:1000 ND 1:100 + Cisatr 1:100 +	Y	Cefazed 1:100 – 1:10 – 1:1 – Lidoc 1:50 – 1:5 – Thiop 1:10 – 1:1 –	Cefazed 1:100000 – 1:10000 – 1:1000 – Lidoc 1:50 – 1:5 – Thiop 1:100 –
19	2012	M	63	Cisatr	2	1:1+	1:100+	ND	Rocur 1:10 – 1:1 – Vecur 1:40 – 1:4 –	Rocur 1:200 ND 1:100 – Vecur 1:400 – 1:40 –	N	Propof 1:1 – Remif 1:1 –	Propof 1:100 – 1:10 – Remif 1:100 – 1:10 –

+, positive; –, negative; Atrac, atracurium; Cefazed, cefazedone; Cisatr, cisatracurium; Etomid, etomidate; Fentan, fentanyl; Flumox, flumoxef; IDT, intradermal test; Levof, levofloxacin; Lidoc, lidocaine; Midaz, midazolam; Moxif, moxifloxacin; N, no; ND, not done; NMBA, neuromuscular blocking agent; Prop, propofol; Remif, remifentanyl; Rocur, rocuronium; SPT, skin prick test; Succin, succinylcholine; Sufent, sufentanil; Thiop, thiopental; Vecur, vecuronium; Y, yes. Undiluted concentration of propofol was 10 mg ml^{-1} , remifentanyl and fentanyl 0.05 mg ml^{-1} , levofloxacin 5 mg ml^{-1} , lidocaine 10 mg ml^{-1} , moxifloxacin 1.6 mg ml^{-1} , flumoxef 10 mg ml^{-1} , thiopental 25 mg ml^{-1} , midazolam 5 mg ml^{-1} , etomidate 2 mg ml^{-1} , sufentanil 0.005 mg ml^{-1} and cefazedone 2 mg ml^{-1} . ^a Onset indicates the time interval between the administration of drug and detection of any clinical signs. ^b Normal reference values for serum tryptase are presented in parentheses.

in a few patients, but in none of these cases were the levels elevated during the reactions (Table 1). The clinical signs and treatment for each event are described in Table 2.

Over the 9-year period, the overall incidence of intraoperative anaphylaxis to all NMBA was 2.6 (95% CI, 1.6 to 4.1) per 100 000 exposures. The incidence of anaphylaxis to rocuronium was calculated as 3.8 (95% CI, 2.2 to

Table 2 Clinical signs and treatment of suspected anaphylaxis events

Case no.	Clinical signs	Treatment	Severity ^a	OP hold	Unplanned ICU admission
1	Severe hypotension (55/36 mmHg), tachycardia (118 from 70 bpm), increased airway pressure (23 from 16 cmH ₂ O)	Intravenous ephedrine, volume expansion	3	N	N
2	Whole body urticaria, hypotension (80/30 mmHg)	Intravenous chlorpheniramine, dexamethasone, phenylephrine, volume expansion	3	N	Y
3	Severe hypotension (22/14 mmHg), tachycardia (134 from 66 bpm), increased airway pressure (21 from 6 cmH ₂ O), desaturation (SpO ₂ 97% from 100%)	Cardiac massage, intravenous ephedrine, phenylephrine, calcium chloride, adrenaline, chlorpheniramine, dexamethasone, continuous infusion of adrenaline and dopamine, volume expansion	4	Y	Y
4	Skin rash, severe hypotension (38/32 mmHg), tachycardia (154 from 78 bpm), increased airway pressure (33 from 15 cmH ₂ O), desaturation (SpO ₂ 91% from 100%)	Intravenous phenylephrine, vasopressin, adrenaline, chlorpheniramine, dexamethasone, continuous infusion of adrenaline, volume expansion	3	Y	Y
5	Whole-body urticaria, hypotension (70/52 mmHg), tachycardia (115 from 64 bpm), increased airway pressure (29 from 20 cmH ₂ O)	Intravenous ephedrine, phenylephrine, adrenaline, chlorpheniramine, dexamethasone, volume expansion	3	N	N
6	Whole-body urticaria, rash, severe hypotension (65/37 mmHg), tachycardia (100 from 58 bpm), increased airway pressure (34 from 19 cmH ₂ O)	Intravenous ephedrine, adrenaline, chlorpheniramine, dexamethasone, volume expansion	3	N	Y
7	Skin rash, severe hypotension (39/29 mmHg), tachycardia (130 from 84 bpm), increased airway pressure (23 from 14 cmH ₂ O), increased oral secretion	Intravenous ephedrine, phenylephrine, adrenaline, chlorpheniramine, dexamethasone, volume expansion	3	Y	Y
8	Whole-body urticaria, rash, severe hypotension (45/20 mmHg), tachycardia (115 from 70 bpm), increased airway pressure (24 from 16 cmH ₂ O), coarse breathing sound	Intravenous ephedrine, phenylephrine, adrenaline, chlorpheniramine, methylprednisolone, volume expansion	3	Y	Y
9	Whole-body urticaria, rash, severe hypotension (34/23 mmHg), tachycardia (144 from 72 bpm), increased airway pressure (up to 21 cmH ₂ O)	Intravenous phenylephrine, chlorpheniramine, dexamethasone, continuous infusion of dopamine, volume expansion	3	Y	Y
10	Whole-body urticaria, hypotension (80/30 mmHg), tachycardia (148 from 80 bpm), increased airway pressure (30 from 20 cmH ₂ O), wheezing	Intravenous adrenaline, chlorpheniramine, dexamethasone, volume expansion, inhaled salbutamol	3	N	N
11	Whole-body urticaria, severe hypotension (60/30 mmHg), tachycardia (115 from 65 bpm), increased airway pressure (up to 22 cmH ₂ O)	Intravenous ephedrine, phenylephrine, chlorpheniramine, dexamethasone, volume expansion	3	N	N
12	Rash at intravenous infusion site, and on face, neck and anterior chest, tachycardia (115 from 65 bpm), increased airway pressure (up to 21 cmH ₂ O), desaturation (SpO ₂ 98% from 100%), increased oral secretion	Intravenous chlorpheniramine	3	N	Y
13	Severe hypotension (41/31 mmHg), tachycardia (124 from 88 bpm), increased airway pressure (40 from 16 cmH ₂ O)	Intravenous ephedrine, phenylephrine, calcium chloride, vasopressin, dexamethasone, volume expansion, inhaled salbutamol	3	N	Y
14	Face flush, severe hypotension (48/24 mmHg), tachycardia (100 from 72 bpm), increased airway pressure (24 from 10 cmH ₂ O)	Intravenous ephedrine, phenylephrine, calcium chloride, vasopressin, adrenaline, chlorpheniramine, methylprednisolone, continuous infusion of adrenaline, volume expansion	3	N	Y
15	Whole-body rash, severe hypotension (36/28 mmHg), tachycardia (150 from 70 bpm)	Intravenous ephedrine, phenylephrine, adrenaline, chlorpheniramine, dexamethasone, hydrocortisone, volume expansion	3	Y	Y
16	Severe hypotension (28/18 mmHg), tachycardia (152 from 70 bpm), increased airway pressure (37 from 14 cmH ₂ O)	Intravenous phenylephrine, adrenaline, chlorpheniramine, hydrocortisone, continuous infusion of noradrenaline, volume expansion	3	Y	Y

Table 2 (continued)

Case no.	Clinical signs	Treatment	Severity ^a	OP hold	Unplanned ICU admission
17	Severe hypotension (68/34 mmHg), tachycardia (102 from 58 bpm), increased airway pressure (25 from 18 cmH ₂ O), desaturation (SpO ₂ 92% from 100%)	Intravenous phenylephrine, calcium chloride, vasopressin, adrenaline, hydrocortisone, continuous infusion of adrenaline and noradrenaline, volume expansion	3	N	Y
18	Whole-body urticaria, rash, severe hypotension (58/40 mmHg), tachycardia (125 from 85 bpm)	Intravenous ephedrine, phenylephrine, chlorpheniramine, hydrocortisone, continuous infusion of dobutamine, volume expansion	3	Y	Y
19	Rash on upper trunk and extremities, severe hypotension (50/30 mmHg), tachycardia (130 from 78 bpm)	Intravenous ephedrine, phenylephrine, adrenaline, chlorpheniramine, continuous infusion of dobutamine, volume expansion	3	N	Y

N, no; OP, operation; SpO₂, peripheral oxygen saturation; Y, yes. ^aSeverity was graded from 1 to 4, with higher scores indicating a more severe reaction.

6.1) per 100 000 exposures. Vecuronium-induced anaphylaxis was the next most common at 0.7 (95% CI, 0.1 to 2.6) per 100 000 exposures, significantly different from the rate for rocuronium ($P = 0.014$). However, when the more recently proposed lower concentrations limits for intradermal testing were applied [rocuronium, 0.05 mg ml⁻¹ (1:200 dilution factor) and vecuronium, 0.04 mg ml⁻¹ (1:100 dilution factor)],^{23,24} the number of positively identified anaphylactic reactions was reduced to nine for rocuronium and none for vecuronium. The resultant 'strict' incidence of anaphylaxis would then be 2.1 (95% CI, 1.0 to 4.0) and zero (95% CI, 0 to 1.3) per 100 000 exposures for rocuronium and vecuronium, respectively ($P = 0.016$). Using these same concentration criteria,^{23,24} the overall number of suspected cases would thus be 10, giving an incidence of intraoperative NMBA anaphylaxis of 1.4 (95% CI, 0.7 to 2.5) per 100 000 exposures.

In our study, anaphylaxis was confirmed only when the clinical guidelines^{2,16–18} and criteria⁹ of the previous studies were all satisfied. However, there were another 14 cases of intraoperative anaphylaxis that were strongly suspected as being due to an NMBA on the grounds of the timing and clinical presentation, but the skin test results for NMBAs were negative (Appendix 1, <http://links.lww.com/EJA/A81>). Including these 14 cases as 'probable' cases, the incidence per 100 000 exposures for all suspected cases of anaphylaxis to all NMBAs is 4.4 (95% CI, 3.0 to 6.2), for rocuronium 6.6 (95% CI, 4.4 to 9.5) and for vecuronium 1.5 (95% CI, 0.4 to 3.7), respectively ($P = 0.002$, rocuronium vs. vecuronium).

The overall incidence of anaphylaxis to NMBAs increased 1.4-fold over the 9-year period of the study

($P = 0.002$). A similar 1.4-fold increase occurred for rocuronium. There were no cases of anaphylaxis to rocuronium between 2005 and 2008, followed by 2.0, 1.9, 7.4, 10.6, 5.6 and 4.0 episodes per 100 000 exposures, per year, from 2009 to 2014, respectively. When we apply the 'strict' skin test concentrations,^{23,24} the annual incidence of intraoperative rocuronium anaphylaxis would be 2.0, 1.9, 5.6, 3.5, 1.9 and 4.0 per 100 000 exposures from 2009 to 2014, representing a 1.3-fold increase over 9 years ($P = 0.077$).

In the 16 cases of anaphylaxis suspected as being due to rocuronium, cross-reactivity to other NMBAs was suggested by skin tests (Table 3): to vecuronium (94%, 15/16), succinylcholine (17%, 2/12), atracurium (38%, 3/8) and cisatracurium (100%, 7/7). In the two vecuronium cases, cross-reactivity was observed to rocuronium (2/2), succinylcholine (0/2), atracurium (0/2) and cisatracurium (2/2). When we apply the 'strict' concentrations,^{23,24} cross-reactions for the nine rocuronium cases were 0/9 for vecuronium, 2/7 (29%) for succinylcholine, 2/5 (40%) for atracurium and 3/3 (100%) for cisatracurium.

Discussion

Between January 2005 and May 2014, rocuronium was the leading NMBA used during general anaesthesia at these two tertiary hospitals in South Korea. The intraoperative anaphylaxis rate associated with rocuronium was significantly higher than that of the second leading NMBA (vecuronium), 3.8 vs. 0.7 per 100 000 exposures or, using the suggested lower skin test concentration, 2.1 vs. 0 per 100 000 exposures, respectively.^{9,34} However, the rocuronium anaphylaxis rate we observed in Korean patients is still much lower than the rates described in the

Table 3 Cross-reactivity to each neuromuscular blocking agent^a

Suspected NMBA	Positive reactions to each NMBA				
	Rocuronium	Vecuronium	Succinylcholine	Atracurium	Cisatracurium
Rocuronium ($n = 16$)	–	15/16	2/12	3/8	7/7
Vecuronium ($n = 2$)	2/2	–	0/2	0/2	2/2
Cisatracurium ($n = 1$)	0/1	0/1	ND	ND	–

ND, not done. ^aData are presented as number of positive result per number tested.

previous studies. By way of comparison, these incidence rates are much lower than other anaesthetic complications, such as failed direct laryngoscopy (about 334 per 100 000)²⁷ or malignant hyperthermia (about 33 per 100 000).²⁸

This is the first reported study to calculate the incidence of intraoperative NMBA anaphylaxis using actual data for drug exposure during anaesthesia. We obtained the number of patients exposed to NMBAs from their electronic record of intraoperative medication orders signed by anaesthetists attending the procedures. In the previous reports, exposure to NMBA has been estimated or extrapolated from market share surveys or from annual sales data on drug ampoules.^{8,9,13–15} Such estimates have limitations in that they do not reflect the true number of patients given a particular drug during anaesthesia. In the two study hospitals, anaesthesiologists usually order their medications electronically using the EMR system intraoperatively. Without an electronic order, drugs would not be delivered to operating theatres and the hospitals would not be reimbursed for the drugs administered. It is unlikely that any drug was administered without an electronic order, or that a drug was not administered despite the presence of an electronic order. Thus, the data from the EMR systems is likely to reflect the true number of patients exposed to each NMBA administered during anaesthesia.

We also searched the EMR for all patients who had undergone skin testing for a suspected reaction to a NMBA and reviewed the EMR of these patients to discover who had received a NMBA. In this manner, our data collection also differs from those of the previous publications that were mainly based on self-reporting or referral systems.^{7,14,15}

Among the available NMBAs, rocuronium was the most frequently used NMBA during general anaesthesia at the two hospitals. We analysed our data using both conventional^{16,20–22} and 'strict'^{23,24} criteria (lower drug concentrations for the skin testing) to assess the likelihood of an anaphylactic reaction to a specific drug. Despite the fact that the drug concentration used for skin tests may have a significant impact on the reported incidence of allergic events, many previous reports do not discuss this aspect.^{2,8,15} Nevertheless, regardless of the test drug concentration chosen, our observation that by far the highest incidence of intraoperative anaphylaxis occurs with rocuronium does not change.

Two patients were noted to have experienced two independent anaphylactic reactions to rocuronium during two consecutive anaesthetics (case 1, also case 13, and case 5, also case 6). As described in the methods earlier, these second reactions were counted as separate independent anaphylactic reactions.

Rocuronium has been frequently incriminated in intraoperative anaphylaxis and concern is rising over its widespread use.^{2,9–13} Among the currently available NMBAs, we observed the highest incidence of intraoperative anaphylaxis with rocuronium, an observation consistent with the previous reports.^{9,13} The increasing use of rocuronium may have contributed to the increasing incidence of anaphylactic reactions.^{11,12,14} In both the hospitals, rocuronium is the predominant NMBA used for endotracheal intubation because of its rapid onset. The practice of injecting a large dose rapidly during induction of general anaesthesia may contribute to the higher incidence of anaphylaxis with rocuronium¹⁵ as compared with vecuronium. In our two institutions, the latter is used primarily in small doses as a maintenance NMBA, rather than in large doses during induction.

In our analyses, we have included three cases with unusually delayed anaphylactic reactions (cases 8, 15 and 17), and it is possible that the anaphylaxis was because of some other cause, such as skin disinfectants or latex. However, although neither disinfectants nor latex were tested in the skin tests and we cannot completely exclude these as possible causes, the NMBAs used during the anaesthetics tested positive, supporting our suspicion of NMBA anaphylaxis during anaesthesia.

During the past decade, data have accumulated suggesting that pholcodine use is related to the high frequency of NMBA anaphylaxis during general anaesthesia.²⁹ To date, we have found no evidence that pholcodine-containing compounds (including over-the-counter products) are used in Korea, and the prevalence of IgE antibodies is very low in Koreans.³⁰ Thus, although we did not assess specific IgE antibody levels directly, IgE sensitization associated with pholcodine exposure does not seem likely to be a factor in our results. It remains a possibility that an as yet unknown substance in the environment could cause prior sensitisation to NMBAs.

Previously, succinylcholine has been labelled as a high-risk agent for anaphylaxis by some^{7,13} (approximately one per 9455 exposures),⁷ but we observed no anaphylactic reactions to succinylcholine during the study period. This finding might be explained by the low use of the agent: 6506 exposures over 9 years (0.9% of all exposures). In the two hospitals, succinylcholine was usually used only for a very limited number of cases, such as a few cases of rapid sequence induction or anticipated airway difficulties. Today, in Korea, many anaesthetists prefer to use high-dose rocuronium and sugammadex as a substitute for succinylcholine in such cases. Considering the expected anaphylaxis rate associated with succinylcholine, the number of exposures was simply too small to evaluate the incidence of anaphylaxis caused by succinylcholine in this study.

On skin testing, we identified a relatively wide range of cross-reactivity rates, which is compatible with the previous reports.^{9,13,14} Interestingly, we found that of all the agents, succinylcholine was the least likely to show a cross-reaction in patients allergic to rocuronium, regardless of the test concentration chosen.^{16,20–24} This observation is consistent with the several previous reports,^{13,14} but not with others.⁹ In our study, all patients with steroidal NMBA anaphylaxis showed cross-reactivity with cisatracurium when the internationally recommended test concentration (1 : 1 for skin prick and 1 : 100 dilution for intradermal test) was used. This level of cross-reactivity is much higher than that found in a previous Australian report, where the cross-reactivity was only 22%.⁹ This difference in cross-reactivity rates may be because of the very low concentration of cisatracurium used (1 : 1000 dilution) for the intradermal skin test in that study.⁹

Our study has some limitations. There were no written protocols in the two hospitals as to how to evaluate patients suspected of experiencing perioperative anaphylaxis, and physicians based their investigations on the clinical situation. It is possible that, although intraoperative anaphylaxis was suspected, the anaesthesiologist or surgeon did not refer the patient for further evaluation or skin testing. Such cases would not have been identified by our methodology. Variations in patient referral or data recording could help to explain the fact that we found no cases at all during the first 4 years of the study and, after a rising incidence, the number of cases began to tail off again near the end of the study. Thus, the true incidence of intraoperative anaphylaxis caused by NMBAs may be underestimated in this study. However, such under-reporting would be unlikely to have a differential effect on a specific NMBA.

Second, in some cases, other possible causes of perioperative anaphylaxis such as latex, disinfectants or antibiotics cannot be completely excluded. Although not explored in our cases, latex anaphylaxis is known to be rare in Korea.³¹ We included cases only if they had a positive skin test result and a plausible time relationship between exposure to the drug and the anaphylactic reactions. Consequently, most of our cases occurred during the induction of anaesthesia, shortly after administration of systemic anaesthetics and NMBAs, but before exposure to latex, disinfectants or antibiotics. In addition, in most cases, almost all likely agents were assessed in the skin testing procedure. Thus, it is unlikely that our findings are biased in this aspect.

Third, because NMBAs induce histamine release,³² false-positive skin tests need to be considered. Measurements of serum drug-specific IgE levels or in-vitro basophil activation testing may be useful to support causality,³³ but these tests were not used in the present study. Although raised serum tryptase levels are

supportive of a diagnosis of anaphylaxis,^{2,16} only a few of our patients had these levels measured. Although the drug concentrations used for the skin tests in this study were higher than in some recent reports,^{9,34} our skin test protocols followed the international consensus testing guidelines in place during the study period.^{16,19} We agree that any further investigations for NMBA anaphylaxis should meet the updated consensus criteria.

Finally, we observed much lower incidences of intraoperative anaphylaxis to NMBAs than those in the previous recent reports.^{9,34} However, these reports^{9,34} were from countries with a high consumption of pholcodine-containing compounds.³⁵ The incidences of perioperative anaphylaxis to NMBAs vary between reporting areas: for rocuronium the anaphylaxis rates quoted per 100 000 exposures are 0.07 to 0.1 in the USA,^{10,15} 0.88 in Scandinavia,²⁶ 8 in Australia⁹ and up to 40 in New Zealand.³⁴ These differences may also arise as a result of genetic or environmental differences among the areas studied, as well as variations in the drug concentrations used for skin tests. We noted several cases where there was a high suspicion of anaphylaxis because of an NMBA but these were not included because of negative skin tests (Appendix 1, <http://links.lww.com/EJA/A81>). Had we included these cases in the final calculations, the incidences of intraoperative NMBA anaphylaxis would have been higher than those presented in this report.

Despite these limitations, our methodology, using the EMR and electronic medication orders, reflect not only the real number of patients receiving specific drugs, but also the real incidence anaphylaxis as identified by skin testing and retrospective examination of the records. Although there may be some debate with regard to the accuracy of data entry into the EMR and the drug concentrations used for skin testing, our results reflect a similar incidence of perioperative anaphylaxis to NMBAs as found in Asian patients.

In conclusion, in two tertiary hospitals in South Korea, the most common NMBA used during anaesthesia, rocuronium, also has the highest incidence of intraoperative anaphylaxis related to NMBAs. Our study findings suggest that prospective investigation for NMBA anaphylaxis should use agreed, standardised skin testing protocols, and this could then make international comparisons easier. Such comparative data may provide further insight into the causes of anaphylaxis as well as indicating ways to reduce and prevent the reactions.

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