Acta Anaesthesiol Scand 2012; **56:** 260–264
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA

Letters to the Editor

Will direct laryngoscopy become an extinct skill?

doi: 10.1111/j.1399-6576.2011.02595.x

Sir,

Andersen et al. demonstrated that tracheal intubation in obese patients could be equally achieved either by using a videolaryngoscope (VLS) or by direct laryngoscopy (DL) with a Macintosh blade.[1] The similar success rate was probably because of proper positioning of the patients before DL.[2] Unfortunately, there has been a recent trend among our trainees to use a VLS as a first choice intubation tool in the obese patient population. There is no doubt that these devices can reflect better laryngeal views when head, neck, and body positioning is suboptimal because axes alignment is not needed.[3] They are, thus, more forgiving than DL when proper positioning was not assured. The routine use of VLSs as a first choice tool instead of DL, however, should be discouraged. This practice will lead to a gradual decrease, and subsequently less experience and confidence, when using DL for tracheal intubation in obese patients. It will risk an eventual loss of the skills needed to perform DL and the maneuvers, including proper positioning, that can be utilized to optimize visualization in this patient population. Andersen et al. are to be congratulated for drawing everybody's attention to these facts.[1]

Conflict of interested: None.

M. El-Orbany

References

1. Andersen LH, Rovsing L, Olsen KS. GlideScope videolaryngoscope vs. Macintosh direct laryngoscope for intubation of morbidly obese patients: a randomized trial. Acta Anaesthesiol Scand 2011; 55: 1090–7.
2. El-Orbany M, Woehlck H, Salem MR. Head and neck position before direct laryngoscopy. Anesth Analg 2011; 113: 103–9.
3. Niforopoulou P, Pantazopoulos I, Demestiha T, Koudouna E, Xanthos T. Video-laryngoscopes in the adult airway management: a topical review of the literature. Acta Anaesthesiol Scand 2010; 54: 1050–61.

Address:
Mohammad El-Orbany
Anesthesiology
Medical College of Wisconsin
9200 W Wisconsin Avenue
Milwaukee, WI 53226
USA
e-mail: elorbany2000@yahoo.com

Sphingosine kinase-signaling pathway: a possible therapeutic target for post-operative cognitive dysfunction

doi: 10.1111/j.1399-6576.2011.02539.x

Sir,

Post-operative cognitive dysfunction (POCD) is a frequent complication after surgery, which affects a wide variety of cognitive domains including memory, executive functioning, and information processing.[1,2] Although the exact pathophysiological mechanisms for POCD remain unclear, increasing data suggests that cytokine-mediated inflammatory mechanisms within the central nervous system contribute to cognitive impairment.[1,2] Inflammation in the brain is characterized by activation of glial cells, expression of key inflammatory mediators, and neurotoxic free radicals.[3] Among them, glial (brain's resident phagocytes of the innate immune system) activation has been implicated as one of the causative factors for neuroinflammation in various neurodegenerative diseases including POCD, Alzheimer's disease, Parkinson's disease, and human immunodeficiency virus associated dementia.[1,3] Consistent with this, Wan et al. has shown that cognitive decline is associated with hippocampal glial activation and increased proinflammatory cytokines in splenectomized rats.[1] Indeed, a role for inflammatory mediators in the development of POCD has been reported, and anti-inflammatory therapy has proved to attenuate POCD in patients undergoing cardiac surgery.[4,5]

It has been well established that sphingosine kinase (SphK)-signaling pathway plays a critical role in the regulation of inflammation, cell proliferation, chemotaxis, immunity, and various pathologic conditions.[6] SphK is a key enzyme in the sphingolipid metabolic pathway, which phosphorylates sphingosine into sphingosine-1-phosphate (S1P). S1P acts extracellularly as a specific and high-affinity ligand for a family of G protein-coupled receptors or an intracellular second messenger. The importance of SphK/S1P in the modulation of inflammation under different pathophysiological conditions has been widely identified. For example, blockade of SphK1 inhibits phagocyte production of endotoxin-induced proinflammatory cytokines and thus improves experimental animal survival rates.[7] More importantly, a recent study has shown that suppression of SphK1 in activated microglia by its inhibitor, N, N dimethylsphingosine, or small interfering RNA resulted in decreased production of proinflammatory cytokines and nitric oxide, and the addition of exogenous S1P to activated microglia enhances their inflammatory responses.[8] The upregulated SphK/S1P in activated microglia has important implications, which raises a possibility that SphK/S1P pathway mediated inflammatory response in microglia is involved in the pathophysiological process of POCD.

Although substantial efforts have been made to identify potential strategies to ameliorate or prevent POCD, significant achievements have not yet been made. If SphK/S1P is involved in the neuroinflammation process as we expected, modulation of

this pathway may be an effective strategy for the prevention and therapy of POCD. Nevertheless, further experimental and clinical studies should be performed to evaluate the precise role of SphK-signaling pathway in POCD.

J. Yang
M. Ji
Z. Zhou
J. Sun
Y. Peng

References

1. Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology 2007; 106: 436–43.
2. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS, Maze M. Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68: 360–8.
3. Dheen ST, Kaur C, Ling EA. Microglial activation and its implications in the brain diseases. Curr Med Chem 2007; 14: 1189–97.
4. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54: 951–6.
5. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, Pagel PS, Warltier DC. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand 2009; 53: 864–72.
6. Spiegel S, Milstien S. Sphingosine-1-phosphate: an enigmatic signalling lipid. Nat Rev Mol Cell Biol 2003; 4: 397–407.
7. Puneet P, Yap CT, Wong L, Lam Y, Koh DR, Moochhala S, Pfeilschifter J, Huwiler A, Melendez AJ. SphK1 regulates proinflammatory responses associated with endotoxin and polymicrobial sepsis. Science 2010; 328: 1290–4.
8. Nayak D, Huo Y, Kwang WX, Pushparaj PN, Kumar SD, Ling EA, Dheen ST. Sphingosine kinase 1 regulates the expression of proinflammatory cytokines and nitric oxide in activated microglia. Neuroscience 2010; 166: 132–44.

Address:
Yong G. Peng
Department of Anesthesiology
Shands Hospital
School of Medicine
University of Florida
Gainesville
FL 32608-0254
USA
e-mail: ufo5201981@gmail.com

'Intense inner agitation': an overlooked side effect of droperidol

doi: 10.1111/j.1399-6576.2011.02582.x

Sir,

Although 40 years have passed since droperidol was first found to be effective for post-operative nausea and vomiting,[1] it continues to be used either separately or in combination with other drugs for this purpose. The major disadvantage of droperidol is its side effects, which include extrapyramidal movements, fatigue, oculogyric crisis and possible life-threatening changes in heart rhythm.

A particularly interesting though somewhat overlooked adverse effect of the butyrophenone derivatives is that of intense inner agitation or *agitation interne prononcée*, as it was originally termed. This was first recognised, in females more so than males, when haloperidol, the parent compound of droperidol, was tried in a volunteer psychiatric study.[2] Later, the situation as well troubled anaesthetists when using droperidol for neuroleptanalgesia (NLA) with as many as 10% of the patients becoming affected.[3] The individuals who had received either of these drugs could suffer a strange and most unpleasant 'locked-in' feeling of restlessness that was difficult for them to describe. Outwardly though, the patient would appear completely normal and so those caring for him or her were unaware of the suffering. Nevertheless, NLA has lost its popularity and is presently seldom, if ever, used for anaesthesia. Because of this, *agitation interne prononcée* has been, to all intents and purposes, forgotten or may even be unfamiliar. One wonders, therefore, how many patients having been given droperidol might indeed be relieved of their nausea and vomiting, but at the price of experiencing this disturbing reaction.

A basic pharmacological premise is that the dose of a drug should never exceed that which is sufficient to fulfil the therapeutic aim intended. The unwanted side effects of droperidol are, without any doubt, dose-related. With this in mind, one could argue against the usual intravenous droperidol dose of 1.25 mg,[4] since 0.75 mg[5] and even 0.25 mg[6] have been shown to be effective for post-operative sickness. Elderly patients would be more likely to experience *agitation interne prononcée* because with ageing, physiological organ function as well as the activity of all body systems are greatly diminished. As a result of this, both the pharmacodynamics and pharmacokinetics become influenced, making this age group more liable to suffer the side effects of droperidol including that described above. Physicians prescribing droperidol should therefore be alerted to the possibility of the occurrence of this sensation, especially when larger doses of the drug are to be administered.

D. A. Cozanitis
P. H. Rosenberg

Acknowledgement

Conflict of interest: none.

References

1. Nikki P, Pohjola S. Nausea and vomiting after ocular surgery. Acta Ophthalmol 1972; 50: 525–31.
2. von Eiff AW, Jesdinsky HJ. Etude clinico-pharmacologique du halopéridol chez personnes normales. Acta Neurol Psychiatr Belg 1960; 60: 63–9.
3. Spreadbury TH. Neuroleptanaesthesia for major surgery (letter). Br J Anaesth 1975; 47: 740.
4. Apfel CC, Cakmakkaya OS, Frings G, Kranke P, Malhotra A, Stader A, Turan A, Biedler A, Kolodzie K. Droperidol has comparable clinical efficiency against both nausea and vomiting. Br J Anaesth 2009; 103: 359–63.
5. Cozanitis D, Asantila R, Eklund P, Paloheimo M. A comparison of ranitidine, droperidol or placebo in the prevention of

nausea and vomiting after hysterectomy. Can J Anaesth 1996; 43: 106–9.
6. Shelly ES, Brown HA. Antiemetic effect of ultra-low dose droperidol. ASA Meeting Abst 1978; 633–4.

Address:
Dimitri A. Cozanitis
Department of Anaesthesiology & Intensive Care Medicine
Helsinki University
Meilahti Hospital
00029 HUS Helsinki
Finland
e-mail: dacozanitis@gmail.com

Recovery of T_1 response following rocuronium induced neuromuscular block reversed by sugammadex

doi: 10.1111/j.1399-6576.2011.02568.x

Sir,

We read with interest the article by Staals et al.[1] recently published in *Acta Anaesthesiologica Scandinavica*, especially the discussion regarding the different mechanism of fade versus that of T_1 which explains the earlier reappearance after sugammadex administration of TOF 0.9 ratio as compared to 90% height of T_1.

The authors claim that before the publication of their article, 'In none of the studies was the recovery of T_1 response reported'.

However, when checking the literature we found an article published in 2009 by Lee et al.[2] in which the primary study endpoint was the recovery time of T_1. Similar to Staals et al., Lee et al. found a slower recovery of T_1 90% as compared to TOF 0.9, though this did not appear to have clinical implications such as prolonged muscle weakness.

Conflict of interest: None.

T. Ezri
D. Trigub
S. Yaakobashvili

References

1. Staals LM, Driessen JJ, Van Egmond J, De Boer HD, Klimek M, Flockton EA, Snoeck MM. Train-of-four ratio recovery often precedes twitch recovery when neuromuscular block is reversed by sugammadex. Acta Anaesthesiol Scand 2011; 55: 700–7.
2. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology 2009; 110: 1020–25.

Address:
Tiberiu Ezri
Department of Anesthesia, Wolfson Medical Center, Holon, 58100, Affiliated to Tel Aviv University
Israel
e-mail: tezri@bezeqint.net

Anaphylaxis to atracurium – a non-QAI-dependent reaction?

doi: 10.1111/j.1399-6576.2011.02598.x

Sir,

Anaphylactic reactions related to neuromuscular blocking agents (NMBA) differ in prevalence between countries, e.g., in Norway, 1/5000 anaesthesias, while in Sweden, 1/83,000 anaesthesias.[1] In Norway, 5–10% of the population was IgE sensitised to morphine (MOR) while in Sweden, no cases were found.[2] MOR carries the NMBA representative allergenic epitope, the quarternary ammonium ion (QAI), although in the tertiary form. The potential sensitiser, pholcodine (PHO), present in a cough depressant, was withdrawn from the Norwegian market in March 2007. Today, the number of reported NMBA anaphylaxis cases IgE sensitised to suxamethonium (SUX) is significantly lower.[3]

In Sweden, one to two cases of anaphylaxis to atracurium (ATRA) is reported each year. Also for ATRA, the QAI is regarded as the allergenic epitope[4] and of patients with ATRA anaphylaxis, 20–40% have IgE antibodies to MOR. Of the four recent Swedish cases, none was IgE sensitised to MOR, PHO (Table 1), or SUX. One case had a positive basophil test, basophil allergen threshold sensitivity (CD-sens),[5] to ATRA but was negative to the other NMBAs. The two patients tested by skin prick test, 0.5–1.0 mg/ml, had a positive test. An ATRA ImmunoCAP (Phadia AB, Uppsala, Sweden) was prepared using tetrahydropapaverine, modified with β-propiolactone, and conjugated to poly L-lysine (ATRA ImmunoCAP conjugate). Two of the four patients had IgE antibodies to this CAP. The IgE binding could

Table 1

Some clinical and immunological characteristics of the four patients with anaphylaxis to ATRA. Tryptase is given as the ratio of the serum level the day of the reaction and that more than 1 day later. Patient C had a higher concentration, 2.1 kU_A/l, of IgE antibodies (IgE-ab) to ATRA 11 months after the reaction than 5 months after, 0.9 kU_A/l.

Patient, age years and sex	Years since anaphylaxis	No. of operations	SPT to ATRA	Tryptase	CD-sens to ATRA	IgE-ab to PHO	IgE-ab to ATRA
A, 37 male	6	2	pos	9.2	neg	neg	neg
B, 67 female	$2^1/_2$	> 25	pos	14.7	neg	neg	0.8
C, 47 female	5/12	> 20	nt	6.9	pos	neg	0.9/2.1
D, 45 female	3/12	0	nt	7.1	neg	neg	neg

SPT, skin prick test; ATRA, atracurium, basophil allergen threshold sensitivity, CD-sens; PHO, pholcodine; neg, negative; pos, positive, nt, not tested.

be completely inhibited by ATRA (10 mg/ml) and the ATRA conjugate (0.4 mg/ml) but not by the other six NMBAs (1–10 mg/ml) or by PHO (10 mg/ml). Sera from three patients with SUX induced anaphylaxis[6] with IgE who had antibodies to SUX, 2–7 kU_A/l, did not react (< 0.1 kU_A/l) the ATRA CAP.

These findings indicate that anaphylaxis to ATRA is IgE antibody mediated but the nature of the allergen is not clear. If it is QAI, the epitope must be exposed in a unique way. PHO is not present in Sweden, and thus some other sensitiser must be involved. Since the two IgE-sensitised patients have been operated several times, they might have been sensitised by repeated exposure to ATRA. However, we do not know in how many of these operations ATRA was used. It is a bit surprising that one of the patients doubled her ATRA IgE antibody level during the period 5–11 months after the operation indicating that, like QAI, the relevant allergen is present in some 'household' chemicals.

In summary, two of the four patients have, most likely, experienced an IgE-mediated anaphylaxis. We would like to put forward a hypothesis that allergic anaphylaxis to ATRA is unrelated to the classical QAI allergen. As a consequence, PHO exposure may not be of importance. The nature of the involved allergenic epitope should be investigated. It is possible that repeated ATRA exposure during anesthesia can induce the IgE sensitisation, but booster stimulation by PHO-related 'household' chemicals containing the ATRA allergen, e.g., cosmetics, cannot be excluded. Further studies are needed to better understand how anaphylaxis to this special NMBA can be diagnosed and prevented.

S.G.O. Johansson
H. Öman
F. Degerbeck
J. Tunelli
E. Florvaag
A. Nopp

References

1. Mertes P-M, Laxenaire MC. Adverse reactions to neuromuscular blocking agents. Curr Allergy Asthma Rep 2004; 4: 7–17.
2. Florvaag E, Johansson SGO, Öman H, Venemalm L, Degerbeck F, Dybendal T, Lundberg M. Prevalence of IgE antibodies to morphine. Relation to the high and low incidence of NMBA anaphylaxis in Norway and Sweden, respectively. Acta Anaesthesiol Scand 2005; 49: 437–44.
3. Florvaag E, Johansson SGO, Irgens Å, de Pater GH. IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. Allergy 2011; 66: 955–60.
4. Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. Nature 1983; 306: 262–4.
5. Johansson SGO, Nopp A, van Hage M, Olofsson N, Lundahl J, Wehlin L, Söderström L, Stiller V, Öman H. Passive IgE-sensitization by blood transfusion. Allergy 2005; 60: 1192–9.
6. Guttormsen AB, Johansson SGO, Öman H, Wilhelmsen V, Nopp A. No consumption of IgE antibody in serum during allergic drug anaphylaxis. Allergy 2007; 62: 1326–30.

Address:
Med.Dr, Professor, *S.G.O. Johansson*
Clinical Immunology and Allergy Unit
Karolinska University Hospital L2:04
S-171 76 Stockholm
Sweden
e-mail: s.g.o.johansson@ki.se

IgE antibody detection in the diagnosis of hypersensitivity to neuromuscular blocking agents

doi: 10.1111/j.1399-6576.2011.02540.x

Sir,

The diagnostic procedure of immediate hypersensitivity reactions to neuromuscular blocking agents (NMBAs) is mainly based upon an evocative clinical history and positive skin tests, and should be supplemented by laboratory assays, such as specific IgE antibody detection.[1] Baldo et al. have demonstrated that substituted ammonium (SA) groups are the major allergenic epitopes of NMBAs.[2] Nevertheless, cross sensitization studies have raised the importance of the accessibility of the SA ions and their adjacent or adjoining structures for IgE binding.[2] IgE detection assays have thus used different providers of SA groups: either single individual NMBAs[3] or generic compounds containing a SA epitope.[4] Furthermore, different strategies exist to detect SA-specific IgE: radioimmunoassays (RIAs) were first developed, while today, fluorescent enzymoimmunoassays (FEIAs) become more popular.

We compared the different available strategies for SA-specific IgE detection in the diagnosis of NMBA allergy. The tested assays are either commercial FEIAs (Phadia, Uppsala, Sweden), directed against single NMBAs (suxamethonium-CAP and rocuronium-CAP) or the SA (tertiary ammonium) structure of morphine (morphine-CAP), or a RIA using quaternary ammonium structures of p-aminophenylphosphoryl-choline (PAPPC-RIA, previously described[4]). Eighteen patients were consecutively investigated (from February 2007 to April 2008) in our outpatient unit on the basis of a suggestive clinical history and a severe allergic reaction (grade III or IV according to the Ring and Messmer classification) and positive skin tests to NMBAs. Culprit molecules were suxamethonium (11 patients), atracurium (2), pancuronium (1), mivacurium (1), cisatracurium (2), or alcuronium (1). Twenty individuals exposed to NMBAs who have experienced anaphylaxis to agents other than NMBAs (antibiotics, latex, and dyes) were used as controls for the study of IgE specificity.

Sensitivity, specificity, positive, and negative predictive values of the different assays are summarized in Fig. 1.

Our first findings confirm the low sensitivity of suxamethonium test (44%, Fig. 1A), as previously described.[5] It is of note that this sensitivity is not improved in patients who experienced anaphylaxis to suxamethonium (45%, Fig. 1B). On the contrary, the sensitivity of the rocuronium assay appears to be excellent, either for the whole population (83%) or for the suxamethonium allergic patients (100%). Unfortunately, this assay is hampered by its low specificity. The other strategy tends to detect IgE against SA residues, either using RIA or FEIA. PAPPC-RIA is known to display excellent characteristics,[4] which is confirmed in our population (Fig. 1). Unfortunately, the use of radioisotopes in this test has limited its wide spreading. Thus, we compared this assay with the recently introduced FEIA morphine-CAP. The new test displays similar performances to the PAPPC-RIA, regardless of the offending NMBA (Fig. 1).

In conclusion, we show, in a limited number of patients, that to detect sensitization against any NMBA, it is more clinically useful to detect specific IgE directed against SA structures than against individual molecules. This is true even if a specific test against the offending drug is used (i.e., suxamethonium). Our results demonstrate the excellent characteristics of the morphine-CAP, in agreement with a recent publication.[6] In our

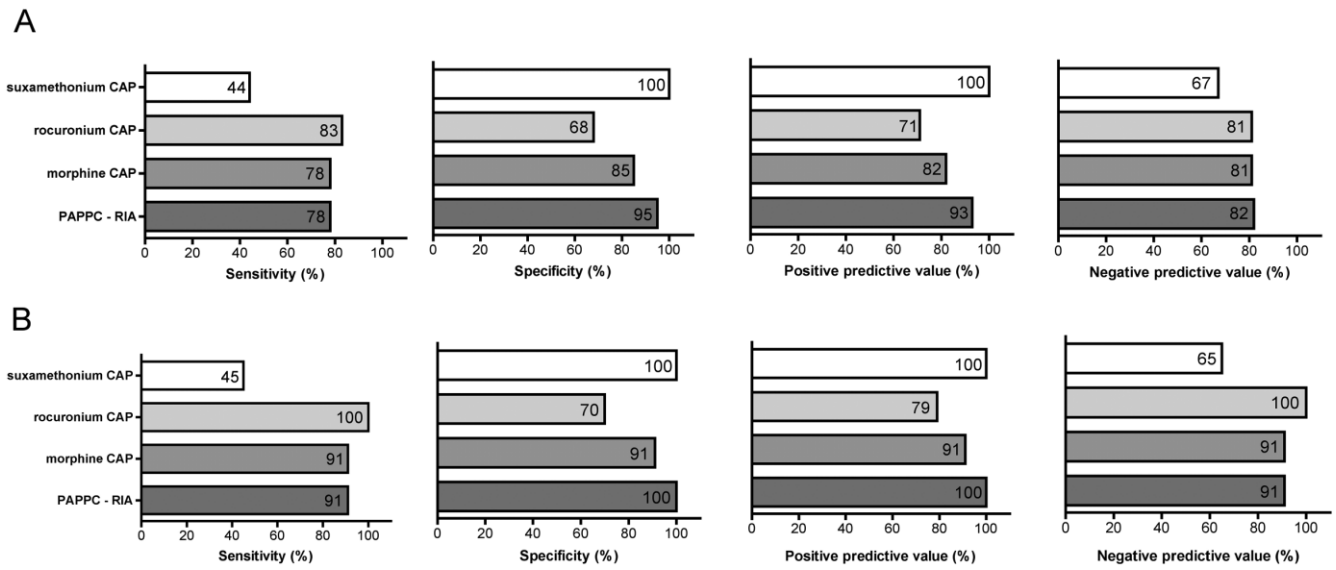

Fig. 1. Characteristics of the different NMBA IgE assays. Sensitivity, specificity, negative, and positive predictive values of the tests are presented for the whole population (A) and for the suxamethonium allergic patients (B). NMBA, neuromuscular blocking agent; PAPPC-RIA, p-aminophenylphosphoryl-choline radioimmunoassay.

hands, the test performed as well as the validated SA provider PAPPC. The good practicability and easy availability of the morphine-CAP will certainly facilitate its widespread use as a routine laboratory test for an efficient diagnosis of NMBA allergy in combination with skin tests.

P. Rouzaire
G. Proton
F. Bienvenu
L. Guilloux
Y. Benoit
V. Piriou
J. Bienvenu
P. Mertes

References

1. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, Demoly P, Working Group for the SFAR; ENDA; EAACI Interest Group on Drug Hypersensitivity. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol 2005; 15: 91–101.
2. Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. Clin Exp Allergy 2009; 39: 325–44.
3. Baldo BA, Fisher MM. Detection of serum IgE antibodies that react with alcuronium and tubocurarine after life-threatening reactions to muscle-relaxant drugs. Anaesth Intensive Care 1983; 11: 194–7.
4. Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. J Allergy Clin Immunol 1992; 90: 153–9.
5. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. Anesthesiology 2005; 102: 897–903.
6. Laroche D, Chollet-Martin S, Leturgie P, Malzac L, Vergnaud MC, Neukirch C, Venemalm L, Guéant JL, Roland PN. Evaluation of a new routine diagnostic test for immunoglobulin E sensitization to neuromuscular blocking agents. Anesthesiology 2011; 114: 91–7.

Address:
Paul Rouzaire
Laboratoire d'Immunologie
Centre de Biologie Sud
CHU Lyon-Sud
69495 Pierre-Bénite
France
e-mail: paul.rouzaire@chu-lyon.fr