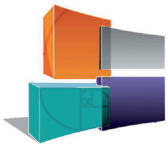
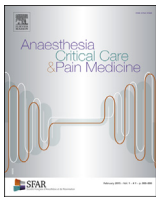
Anaesth Crit Care Pain Med 39 (2020) 125–142



SFAR
Société Française d'Anesthésie et de Réanimation



Guidelines

Guidelines on muscle relaxants and reversal in anaesthesia☆,☆☆

Benoît Plaud [a,*,1], Christophe Baillard [b,1], Jean-Louis Bourgain [c], Gaëlle Bouroche [d], Laetitia Desplanque [e], Jean-Michel Devys [f], Dominique Fletcher [g,2], Thomas Fuchs-Buder [h], Gilles Lebuffe [i], Claude Meistelman [h], Cyrus Motamed [c], Julien Raft [j], Frédérique Servin [e], Didier Sirieix [k], Karem Slim [l], Lionel Velly [m,2], Franck Verdonk [n], Bertrand Debaene [o,1]

[a] *Université de Paris, Assistance publique–Hôpitaux de Paris, service d'anesthésie et de réanimation, hôpital Saint-Louis, 1, avenue Claude-Vellefaux, 75010 Paris, France*
[b] *Université de Paris, Assistance publique–Hôpitaux de Paris, service d'anesthésie et de réanimation, hôpital Cochin-Port Royal, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[c] *Institut Gustave-Roussy, service d'anesthésie, 114, rue Édouard-Vaillant, 94800 Villejuif, France*
[d] *Centre Léon-Bérard, service d'anesthésie, 28, promenade Léa-et-Napoléon-Bullukian, 69008 Lyon, France*
[e] *Assistance publique–Hôpitaux de Paris, service d'anesthésie et de réanimation, hôpital Bichat–Claude-Bernard, 46, rue Henri-Huchard, 75877 Paris cedex, France*
[f] *Fondation ophtalmologique Adolphe-de-Rothschild, service d'anesthésie et de réanimation, 29, rue Manin, 75019 Paris, France*
[g] *Université de Versailles–Saint-Quentin-en-Yvelines, Assistance publique–Hôpitaux de Paris, hôpital Ambroise-Paré, service d'anesthésie, 9, avenue Charles-de-Gaulle, 92100 Boulogne-Billancourt, France*
[h] *Université de Lorraine, CHU de Brabois, service d'anesthésie et de réanimation, rue du Morvan, 54511 Vandœuvre-lès-Nancy, France*
[i] *Université de Lille, hôpital Huriez, service d'anesthésie et de réanimation, rue Michel-Polonovski, 59037 Lille, France*
[j] *Institut de cancérologie de Lorraine, service d'anesthésie, 6, avenue de Bourgogne, 54519 Vandœuvre-lès-Nancy, France*
[k] *Groupe polyclinique Marzet-Navarre, service d'anesthésie, 40, boulevard d'Alsace-Lorraine, 64000 Pau, France*
[l] *Université d'Auvergne, service de chirurgie digestive et hépatobiliaire, hôpital d'Estaing, 1, rue Lucie-Aubrac, 63100 Clermont-Ferrand, France*
[m] *Université Aix-Marseille, hôpital de la Timone adultes, service d'anesthésie et de réanimation, 264, rue Saint-Pierre, 13385 Marseille cedex 05, France*
[n] *Sorbonne université, hôpital Saint-Antoine, 84, rue du Faubourg-Saint-Antoine, 75012 Paris, France*
[o] *Université de Poitiers, service d'anesthésie et de réanimation, CHU de Poitiers, BP 577, 86021 Poitiers cedex, France*

ARTICLE INFO

Article history:
Available online 8 January 2020

Keywords:
Muscle relaxants
Reversal
Neuromuscular
Monitoring
Update of expert guidelines

ABSTRACT

Objectives: To provide an update to the 1999 French guidelines on "*Muscle relaxants and reversal in anaesthesia*", a consensus committee of sixteen experts was convened. A formal policy of declaration and monitoring of conflicts of interest (COI) was developed at the outset of the process and enforced throughout. The entire guidelines process was conducted independently of any industrial funding (i.e. pharmaceutical, medical devices). The authors were required to follow the rules of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE®) system to assess the quality of the evidence on which the recommendations were based. The potential drawbacks of making strong recommendations based on low-quality evidence were stressed. Few of the recommendations remained ungraded.

Methods: The panel focused on eight questions: (1) In the absence of difficult mask ventilation criteria, is it necessary to check the possibility of ventilation via a facemask before muscle relaxant injection? Is it necessary to use muscle relaxants to facilitate facemask ventilation? (2) Is the use of muscle relaxants necessary to facilitate tracheal intubation? (3) Is the use of muscle relaxants necessary to facilitate the insertion of a supraglottic device and management of related complications? (4) Is it necessary to monitor neuromuscular blockade for airway management? (5) Is the use of muscle relaxants necessary to facilitate interventional procedures, and if so, which procedures? (6) Is intraoperative monitoring of neuromuscular blockade necessary? (7) What are the strategies for preventing and treating residual neuromuscular blockade? (8) What are the indications and precautions for use of both muscle relaxants and reversal agents in special populations (e.g. electroconvulsive

☆ Updated guidelines from the French Society of Anaesthesia & Intensive Care Medicine (Société française d'anesthésie et de réanimation – SFAR).
☆☆ Text approved by the SFAR's board of directors (21/06/2018) and presented at the SFAR's annual meeting (29/09/2018).
* Corresponding author.
E-mail address: benoit.plaud@aphp.fr (B. Plaud).
[1] SFAR expert coordinators.
[2] Organisers.

https://doi.org/10.1016/j.accpm.2020.01.005

therapy, obese patients, children, neuromuscular diseases, renal/hepatic failure, elderly patients)? All questions were formulated using the Population, Intervention, Comparison and Outcome (PICO) model for clinical questions and evidence profiles were generated. The results of the literature analysis and the recommendations were then assessed using the GRADE® system.

Results: The summaries prepared by the SFAR Guideline panel resulted in thirty-one recommendations on muscle relaxants and reversal agents in anaesthesia. Of these recommendations, eleven have a high level of evidence (GRADE 1±) while twenty have a low level of evidence (GRADE 2±). No recommendations could be provided using the GRADE® system for five of the questions, and for two of these questions expert opinions were given. After two rounds of discussion and an amendment, a strong agreement was reached for all the recommendations.

Conclusion: Substantial agreement exists among experts regarding many strong recommendations for the improvement of practice concerning the use of muscle relaxants and reversal agents during anaesthesia. In particular, the French Society of Anaesthesia and Intensive Care (SFAR) recommends the use of a device to monitor neuromuscular blockade throughout anaesthesia.

SFAR organisers and expert coordinators

Christophe Baillard, Bertrand Debaene, Benoît Plaud

Organising committee

Dominique Fletcher, Lionel Velly

SFAR experts group

Christophe Baillard, Jean-Louis Bourgain, Gaëlle Bouroche, Bertrand Debaene, Jean-Michel Devys, Thomas Fuchs-Buder, Gilles Lebuffe, Claude Meistelman, Cyrus Motamed, Benoît Plaud, Julien Raft, Frédérique Servin, Didier Sirieix, Karem Slim

Reading group

SFAR Guidelines committee: Julien Amour, Alice Blet, Gérald Chanques, Vincent Compère, Philippe Cuvillon, Fabien Espitalier, Marc Garnier, Etienne Gayat, Hervé Quintard, Bertrand Rozec, Lionel Velly, Emmanuel Weiss

SFAR board of directors: Xavier Capdevila, Hervé Bouaziz, Laurent Delaunay, Pierre Albaladejo, Jean-Michel Constantin, Marie-Laure Cittanova-Pansard, Marc Léone, Bassam Al Nasser, Valérie Billard, Francis Bonnet, Julien Cabaton, Marie-Paule Chariot, Isabelle Constant, Alain Delbos, Claude Ecoffey, Jean-Pierre Estèbe, Marc Gentili, Olivier Langeron, Pierre Lanot, Luc Mercadal, Karine Nouette-Gaulain, Jean-Christian Sleth, Eric Viel, Paul Zetlaoui

1. Introduction

The consensus conference (CC) on "*indications for muscle relaxant use in anaesthesia*" was conducted in 1999 and its findings were published in 2000 [1]. It specified the conditions of use of muscle relaxants for endotracheal intubation and surgical intervention, as well as their side effects and the safety rules during perioperative use of muscle relaxants and reversal agents. The target populations were adults and children. Muscle relaxant use was also discussed at other CCs and expert conferences (ECs), including those on airway control: "*Airway management during adult anaesthesia, other than for difficult intubation*" [2], "*Difficult intubation*" [3], "*Pre-hospital sedation and analgesia*" [4], and "*Sedation and analgesia in resuscitation*" [5].

These reference documents argued in favour of the positive effects of muscle relaxant use on intubation conditions for both health care providers and patients, particularly in adults.

Several new elements have emerged since this initial CC on the "*indications for muscle relaxant use in anaesthesia*" [1], such as:

- the possibility of administering a non-depolarising muscle relaxant, both with and without prior verification of the ability to provide effective ventilation via a mask;
- the positive effects of muscle relaxant use on intubation conditions for both health care providers and patients, including in paediatrics and electroconvulsive therapy;
- the development of alternatives to intubation such as supraglottic devices to achieve airway control;
- the rise of laparoscopic surgery, with and without robotic assistance;
- regularly updated epidemiological data concerning allergic risk associated with muscle relaxants, which were reviewed in the formalised expert recommendations on "*Reducing the risk of anaphylaxis during anaesthesia*" [6];
- recent data on precautions for use of suxamethonium that led to a modification of the Summary of Product Characteristics (SPC) by the Agence nationale de sécurité du médicament et des produits de santé (ANSM) [7];
- market withdrawal of certain muscle relaxant compounds (pancuronium, vecuronium) and the availability of cisatracurium;
- epidemiological assessment of morbidity-mortality related to non-compliant practices in rapid-sequence induction (anaesthesia, emergency and pre-hospital settings);
- the positive impact of neuromuscular monitoring on management of neuromuscular blockade, poor performance of clinical reversal tests for the detection of residual neuromuscular blockade;
- regular international updating of data on the frequency of residual neuromuscular blockade, with and without pharmacological reversal, and consequences of the latter being associated with excess risk of severe morbidity immediately following anaesthesia;
- the development of new methods for objective neuromuscular blockade monitoring for routine clinical use;
- review of the effects of neostigmine, especially in terms of timing and required spontaneous recovery, time-to-peak effect;
- the possibility of dose reduction in certain cases and initial data on the use of sugammadex, a selective reversal agent for steroidal muscle relaxants.

Regarding the risk–benefit ratio relative to the use of muscle relaxants, the experts remind us that, for more than thirty years now, all studies investigating intraoperative allergic accidents in France have been pointing in the same direction. Muscle relaxants have been involved in over half of these accidents [8,9]. Among these muscle relaxants, rocuronium and suxamethonium have been more frequently incriminated than others. In the study by Mertes et al. [10], for 373 cases of documented allergy to muscle relaxants, rocuronium was involved in 16 cases and suxamethonium in 226 cases. Taking market share into consideration, rocuronium was responsible for 4.6% of accidents involving allergy to muscle relaxants, whilst representing only 1.1% of the market share. Suxamethonium, with a market share of 12.2%, was responsible for 60.6% of accidents involving allergy to muscle relaxants. By comparison, atracurium has a market share of 45.2% and is responsible for 19.6% of accidents involving allergy to muscle relaxants. Also considering market share, the frequency of rocuronium anaphylaxis was estimated at 8.0/100,000 administrations, *vs.* 2.8/100,000 for vecuronium and 4.0/100,000 for atracurium. The incidence for suxamethonium could not be determined [11,12]. More recently, the frequency of anaphylaxis due to atracurium has been estimated at 1/22,451 administrations *vs.* 1/2080 for suxamethonium and 1/2499 for rocuronium [13]. French pharmacovigilance centres (unpublished data transcribed with the permission of the ANSM) have confirmed these data. Out of 1624 cases analysed, only those with positive tryptase and skin tests were selected, i.e. 680 cases. Suxamethonium had a notification rate of 7.05/100,000 administrations *vs.* 4.15/100,000 for rocuronium. Other muscle relaxants had notification rates of 0.17/100,000 to 0.36/100,000. Two distinct groups were confirmed: suxamethonium and rocuronium, which had higher notification rates, and other muscle relaxants, which had lower notification rates.

2. Methods

Literature search and selection criteria

The literature search focused on publications referenced in Medline® and the Cochrane database® with no time limits. The selection focused on controlled trials, meta-analyses, systematic reviews and cohort studies. A specific analysis of the paediatric literature was carried out.

Population and comparisons

The populations under study included adults, children and special populations such as obese patients, patients with renal/hepatic dysfunction, and patients with neuromuscular diseases. These different situations are analysed separately.

The GRADE® system

Each question was formulated using the Patients, Intervention, Comparison and Outcome (PICO) model. The method used to develop the recommendations is the Grading of Recommendations, Assessment, Development and Evaluation (GRADE®) system. After a quantitative analysis of the literature, this method allows separate determination of the quality of the evidence, i.e. an estimation of the confidence that may be had in analysing the effects of the quantitative intervention, as well as a recommendation level. Quality of evidence was divided into four categories:

- high: future research will most likely not change confidence in the estimated effect;
- moderate: future research is likely to change confidence in the estimated effect and might alter the estimated effect itself;
- low: future research will most likely have an impact on confidence in the estimated effect and will probably alter the estimate of the effect itself;
- very low: the estimated effect is very uncertain.

A quality-of-evidence analysis was conducted for each study and an overall level of evidence was defined for a given question and criterion. The final formulation of the recommendations will always be binary, i.e. either positive or negative and either strong or weak:

- strong recommendation: we recommend/do not recommend (GRADE 1+ or 1−);
- weak recommendation: we suggest/do not suggest (GRADE 2+ or 2−).

The strength of a recommendation is influenced by key factors and validated through voting by the experts using the Delphi method and GRADE® grids:

- estimate of the effect;
- overall level of evidence: the higher the level, the stronger the recommendation;
- the balance between desirable and adverse effects: the more favourable the balance, the higher the recommendation. The narrower the gradient, the more likely a weak recommendation is warranted;
- values and preferences: in the event of uncertainties or great variability, the recommendation will most likely be weak. These values and preferences must be obtained directly from the people involved (patient, doctor, decision-maker);
- costs: the higher the costs or the use of resources, the weaker the recommendation;
- to develop a recommendation, at least 50% of participants must have one opinion and less than 20% the opposite opinion;
- to develop a strong recommendation, at least 70% of participants must agree (grade between 7 and 10).

In some cases, it was impossible to propose a recommendation.

If the experts did not have enough data from the literature to allow them making a recommendation, an expert opinion was then proposed and, if at least 70% of the experts agreed with the proposal, it was approved.

The summaries prepared by the experts and application of the GRADE® system resulted in thirty-one recommendations being made. Among the formalised recommendations, eleven have a high level of evidence (GRADE 1±) and twenty have a low level of evidence (GRADE 2±). For five recommendations, the GRADE® method could not be applied, and expert advice was provided for two of them. After two rounds of scoring and an amendment, strong agreement was reached for all the recommendations.

These French Expert Recommendations (FERs) supersede the previous recommendations from the French Society of Anaesthesia & Intensive Care Medicine (SFAR) and have the same scope. The SFAR encourages all anaesthetists to comply with these FERs to ensure the quality of patient care. However, in applying these recommendations, individual practitioners must exercise their own judgment, based on their personal expertise and the specific features of their institution, when determining the intervention method best suited to the actual condition of their patients.

The questions tackled in these Guidelines updates are as follows:

- in the absence of difficult mask ventilation criteria is it necessary to check the possibility of ventilation via a facemask before muscle relaxant injection? Is it necessary to use muscle relaxants to facilitate facemask ventilation?
- is the use of muscle relaxants necessary to facilitate tracheal intubation?

- is the use of muscle relaxants necessary to facilitate the insertion of a supraglottic device and management of related complications?
- is it necessary to monitor neuromuscular blockade for airway management?
- is the use of muscle relaxants necessary to facilitate interventional procedures, and if so, which procedures?
- is intraoperative monitoring of neuromuscular blockade necessary?
- what are the strategies for preventing and treating residual neuromuscular blockade?
- what are the indications and precautions for use of both muscle relaxants and reversal agents in special populations?

Question 1: In the absence of difficult mask ventilation criteria is it necessary to check the possibility of ventilation via a facemask before muscle relaxant injection? Is it necessary to use muscle relaxants to facilitate facemask ventilation?

PICO. P = "adult patients receiving muscle relaxants for surgery involving tracheal intubation", I = "muscle relaxants (muscle relaxant type: suxamethonium, atracurium, vecuronium and rocuronium)", C = "no muscle relaxants", O = "measurement of respiratory mechanical parameters (VT, insufflation pressure)". For the question "Is it necessary to use muscle relaxants to facilitate face mask ventilation?", O = "quality scale for face mask ventilation."

R1.1 – It is probably not recommended to verify the possibility of mask ventilation before administering a muscle relaxant.
(GRADE 2−) STRONG AGREEMENT

R1.2 – It is probably recommended to administer a muscle relaxant to facilitate facemask ventilation.
(GRADE 2+) STRONG AGREEMENT

Rationale

Safety is provided by the use of oxygenation methods immediately available prior to the onset of desaturation ($SpO_2 < 95\%$). Regardless of the induction protocol, with or without a muscle relaxant, the safety margin between apnoea duration and O_2 reserves is small. This situation is all the more common with a high body mass index and high O_2 consumption. Testing mask ventilation quality before injecting a muscle relaxant increases the duration of induction by adding the time it takes for the muscle relaxant to work to that of the other anaesthetic agents.

Testing the quality of mask ventilation before administering a muscle relaxant may be proposed bearing in mind that:

- injecting a muscle relaxant may lengthen the duration of apnoea and induce desaturation due to the inability to ventilate with the mask;
- it must be possible to wake up the patient at any time if the situation so warrants.

The need to wake up a patient due to the inability to intubate is extremely rare and poorly documented: there have been only two cases out of 100 difficult intubations among 11,257 intubations [14] and nine cases among 698 patients with both difficult intubation and mask ventilation [15]. Rapid recovery of spontaneous ventilation after induction does not prevent the occurrence of oxygen desaturation [16], which justifies maintaining a high O_2 reserve at all times.

Neuromuscular blockade does not necessarily increase apnoea duration and risk of desaturation. Following administration of thiopental and suxamethonium in healthy volunteers, four out of twelve subjects showed a decrease in oxygen saturation to below 80% before recovery of neuromuscular blockade. Among twenty-four healthy volunteers, injection of propofol 2.0 mg/kg and remifentanil 1.5 or 2.0 μg/kg resulted in profound desaturation in five subjects (four in the 2.0 μg/kg group and one in the 1.5 μg/kg group) [17]. Increasing the dose of remifentanil from 1.0 to 2.0 μg/kg increased apnoea time substantially (270 s to 487 s) while around 10% of patients had intubation conditions deemed unacceptable [18]. Using remifentanil at a dose of 4 μg/kg provides intubation conditions comparable to those observed after suxamethonium at the expense of blood pressure lowering, and an increase in duration of apnoea (12.8 min *vs.* 6.0 min) [19]. All publications report the use of propofol at doses between 2.0 and 2.5 mg/kg. The return to consciousness judged on the response to simple orders and the bi-spectral index (BIS) is 529 s (standard deviation 176 s) after injecting 2 mg/kg of propofol [20]. Nevertheless, awakening does not imply disappearance of the effects of propofol on the laryngeal muscles; the latter remain measurable for concentrations of as low as 0.7 μg/mL [21]. The effect of suxamethonium has been evaluated as lasting seven to eight minutes long using laryngeal and diaphragmatic electromyography [22] and about twelve minutes using accelerometery [23], with significant variability in both cases.

Reducing the dose of suxamethonium does not significantly shorten this apnoea time [24]. Use of sugammadex after rocuronium results in a faster and more reliable recovery time than use of suxamethonium [23], if the right number of vials of sugammadex is immediately available [25]. Injecting sugammadex after rocuronium gives better results than suxamethonium in terms of mean value (4.7 min) and individual variability [23]. Neuromuscular blockade reversal using sugammadex may be ineffective and lead to a situation requiring emergency tracheal access [26].

Does a muscle relaxant impair mask ventilation in patients without difficult mask ventilation criteria and/or difficult intubation? Muscle relaxant administration improves muscle relaxation especially when using high doses of sufentanil [27] or remifentanil [28] or low doses of a hypnotic [29]. Five studies investigated the effect of muscle relaxant injection on respiratory mechanics, and all used different criteria. Two of these included a small number of patients (30 and 32, respectively) and reported non-significant [30] or slightly significant results in favour of suxamethonium [31]. Interindividual variability in muscle relaxant response is important, suggesting that some patients are already fully relaxed before paralysis. In two studies (125 patients, some of whom were obese [32], and 210 patients [33]), the improvement in ventilation after neuromuscular blockade was significant, although impairment was seen in 19% of them [33]. Improved mask ventilation was also brought to light on objective criteria after injecting rocuronium [34].

Based on a database of four hospitals including 492,239 general anaesthesias, the combination of mask ventilation difficulty and intubation difficulty was reported in 698 patients (0.4%) [15]. Improved mask ventilation after neuromuscular blockade was observed for 19 patients, with no worsening. In a prospective series of 12,225 patients with difficult intubation criteria, improved ventilation after muscle relaxant injection was noticed in 56 out of 90 patients presenting difficult mask ventilation (with no impairment for the others) [35].

Question 2: Is the use of muscle relaxants necessary to facilitate tracheal intubation?

PICO. P = "adult patients receiving muscle relaxants for a scheduled procedure with tracheal intubation", I = "muscle

relaxants (muscle relaxant type: suxamethonium, atracurium, cisatracurium, mivacurium, pancuronium, rapacuronium, vecuronium and rocuronium)", C = "no muscle relaxants", O = either positive, for "assessment of intubation conditions, either by the criteria of Cormack and Lehane" [36,37] or those of the "Good Clinical Research Practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" [38], or negative, for "upper respiratory discomfort: sore throat, hoarseness, vocal cord injury, pharyngeal injury, dental injury, severe complications: tracheal perforation, oesophageal intubation, inhalation lung disease, allergic reaction."

R2.1 – The use of a muscle relaxant is recommended to facilitate tracheal intubation.
(GRADE 1+) STRONG AGREEMENT

Rationale

Since the 1999 consensus conference, several studies have examined the issue of whether muscle relaxants facilitate tracheal intubation. To this end, thirty-two randomised and controlled studies, a cohort study and a systematic review were analysed [19,39–70]. The muscle relaxants currently available in France (from the oldest to the most recent) are suxamethonium, atracurium, rocuronium, mivacurium and cisatracurium. Studies involving doses of muscle relaxant below the 95% effective dose (ED_{95}) at the adductor pollicis were not considered. If several doses of the same muscle relaxant were used per study, the dose closest to twice the ED_{95} was retained. For those studies comprising several protocols without a muscle relaxant, a second analysis was conducted considering only the best protocol. This is how data from 1247 patients who had received a muscle relaxant and 1422 who had not received a muscle relaxant (best protocol analysis: 1092 patients) were analysed for a total of 2669 patients (best protocol analysis: 2339 patients). Without a muscle relaxant, 350 patients (best protocol analysis: 283 patients) presented poor intubating conditions. This corresponds to a rate of 24.6% (best protocol analysis: 25.9%). With a muscle relaxant, 51 patients (4.1%) had poor intubating conditions. The cohort involved 103,784 patients, of whom 28,201 were intubated without and 75,583 with a muscle relaxant. Without a muscle relaxant, the rate of poor intubating conditions was 6.7% *vs.* 4.5% using a muscle relaxant. This study identified muscle relaxant-free intubation as an independent risk factor for difficult intubation. As a result, these data support the concept that, compared with a muscle relaxant-free protocol, the use of a muscle relaxant facilitates tracheal intubation.

R2.2 – The use of a muscle relaxant is recommended to reduce pharyngeal and/or laryngeal injury.
(GRADE 1+) STRONG AGREEMENT

Rationale

The quality of intubation can have clinical consequences for the patient. Mencke et al. [56] established a link between intubation quality and postoperative complications such as vocal cord damage and hoarseness. Six randomised controlled studies in 746 patients (best protocol analysis: 694 patients) were analysed [42,43,45,56,57,66]. According to these studies, 90 patients (best protocol analysis: 65 patients) sustained pharyngeal and/or laryngeal injuries. This corresponds to a rate of 22.6% (best protocol analysis: 18.7%). By using a protocol with a muscle relaxant, this incidence could be reduced to 9.7%. This reduction in pharyngeal and/or laryngeal lesions was seen in all six studies analysed. The absence of a muscle relaxant to facilitate intubation increases the risk of upper respiratory injury or discomfort. While a pharyngeal and/or laryngeal injury rate of nearly 10% despite good intubating conditions may be surprising, these complications may be caused by several factors other than intubating conditions. The most important are certainly the tracheal tube size and extubation conditions.

R2.3 – Administration of a short-acting muscle relaxant for rapid-sequence induction is probably recommended.
(GRADE 2+) STRONG AGREEMENT

Rationale

Rapid-sequence induction, whatever the indication, consists of minimising the time between loss of consciousness and correct insertion of the tracheal tube in order to avoid positive pressure ventilation via the face mask and prevent the risk of inhaling gastric content. To achieve this goal, the fastest acting anaesthetic drugs are preferred. When a neuromuscular blocking drug is associated to facilitate tracheal intubation, it must meet the same requirement, i.e. generate paralysis within the shortest possible onset time. Suxamethonium is traditionally used in this indication because it has the shortest onset time and the shortest duration of action of all available muscle relaxants. It has numerous side effects, some of which are serious. Rocuronium is the non-depolarising muscle relaxant with the shortest onset time and has been proposed as an alternative to suxamethonium. A meta-analysis of the Cochrane Library analysed and compared the intubating conditions arising after administration of suxamethonium and rocuronium [8]. Fifty publications (controlled and randomised trials or controlled clinical trials) involving 4151 patients were analysed. Suxamethonium provides excellent intubation conditions more frequently than rocuronium (RR = 0.86; 95% confidence interval: 0.81–0.92; I^2 = 72%). In a subgroup analysis comparing suxamethonium 1.0 mg/kg with rocuronium at a dose greater than 0.9 mg/kg, no superiority of suxamethonium was found. However, the heterogeneity noted between the different studies warrants a GRADE 2 level for the recommendation.

Question 3: Is the use of muscle relaxants necessary to facilitate the insertion of a supraglottic device and management of related complications?

PICO. P = "adult patients receiving muscle relaxants for a scheduled procedure involving a supraglottic device", I = "muscle relaxants (muscle relaxant type: suxamethonium, atracurium, vecuronium and rocuronium)", C = "no muscle relaxants or before – after", O = "measurement of respiratory mechanical parameters (VT, insufflation pressure) and success rate of laryngeal mask positioning or recovery of airway patency".

R3.1 – Routine use of a muscle relaxant to facilitate insertion of a supraglottic device is probably not recommended.
(GRADE 2–) STRONG AGREEMENT

Rationale

Without muscle relaxant, the success rate of laryngeal mask insertion is commonly high and ventilation conditions are often satisfactory [71,72]. Neuromuscular blockade is probably useful when inserting a supraglottic device when the doses of hypnotic and opioid agents used for induction are low [73,74]. Anaesthesia protocols that exclude propofol as an induction agent have a high

rate of adverse insertion events whose incidence decreases with neuromuscular blockade [75,76]. No publications have reported any adverse effects of neuromuscular blockade on the quality of ventilation. The overall level of evidence in the literature remains low due to the heterogeneity of the anaesthesia protocols used and their outcomes.

R3.2 – Administration of a muscle relaxant in case of airway obstruction related to a supraglottic device is probably recommended.

(GRADE 2+) STRONG AGREEMENT

Rationale

In the event of upper airway obstruction, administering a muscle relaxant is proposed in the same way as a change in supraglottic device size or adjustment of position [77]. Two clinical entities must be distinguished: glottic closure resulting in incomplete or easily reversible obstruction, and laryngospasm involving complete glottic closure which is irreducible using the standard methods of ventilation [78]. Muscle relaxation is highly recommended during laryngospasm even if injection of propofol (0.25 to 0.8 mg/kg) is effective in the majority of cases (77%) [79]. In the absence of a muscle relaxant, muscle relaxation under general anaesthesia is not always complete. Moreover, opioids tend to increase muscle tone [28]. In the event of glottic closure not related to laryngospasm, the administration of a muscle relaxant is useful after providing sufficiently deep anaesthesia. The best agent is suxamethonium, which is effective in all cases [80]. In addition, it is fast-acting, and the laryngeal muscles are particularly sensitive to it [81]. It is most often given intravenously (1.0 mg/kg) but intramuscular and even sublingual administrations have been proposed (4.0 mg/kg) [82,83]. In children under three years of age, atropine (0.02 mg/kg) is usually associated to avoid bradycardia or even cardiac arrest [80]. It is essential to be aware of the adverse effects of suxamethonium and to comply with the contraindications of the drug [82,84]. Comparable efficacy may possibly be achieved with a non-depolarising muscle relaxant because low concentrations of muscle relaxant are required to relax the laryngeal muscles [84]. A low dose is sufficient to achieve glottic opening if the depth of anaesthesia is adequate (rocuronium or atracurium 0.1 to 0.2 mg/kg) [28,85]. In all cases, reduction of complications associated with upper airway obstruction is optimised when it is integrated within a quality approach. The immediate availability of suxamethonium and atropine, especially in paediatric operating theatres, is crucial as when combined with neuromuscular blockade for intubation, it reduces the incidence of cardiac arrest and severe airway obstruction accidents nearly by half [86].

Question 4: Is it necessary to monitor neuromuscular blockade for airway management?

PICO. P = "adult patients receiving non-depolarising muscle relaxants for a scheduled procedure with tracheal intubation", I = "muscle relaxants (muscle relaxant type: atracurium and rocuronium)", C = "no monitoring", O = "assessment of intubation conditions, using either the Cormack & Lehane criteria [36,37] or those of Good Clinical Research Practice (GCRP) in Pharmacodynamic Studies of Neuromuscular Blocking Agents" [38].

No recommendation - Data in the literature are insufficient to establish any recommendations on the use of instrumental monitoring of neuromuscular blockade during tracheal intubation.

Rationale

There are no studies supporting a recommendation concerning the relevance of neuromuscular monitoring for intubation compared to a fixed time following injection of rocuronium or atracurium.

R4.1 – The experts suggest that if instrumental neuromuscular blockade monitoring is used, the selected site should be the corrugator supercilii muscle because of its sensitivity to muscle relaxants and its kinetics of neuromuscular blockade, which are comparable to those of laryngeal muscle.

EXPERT OPINION

Rationale

Intubating conditions are worse when the orbicularis oculi is used to decide when to perform tracheal intubation compared to when the corrugator supercilii or the adductor pollicis are used [87,88]. Poor intubating conditions are only found in the group of patients with orbicularis oculi monitoring. The onset time of maximum neuromuscular blockade at the corrugator supercilii is comparable to that of the laryngeal adductor muscles, whereas that of the orbicularis oculi corresponds much more closely to those of muscles which are more sensitive to muscle relaxants (e.g. adductor pollicis) [89]. Under the same intubating conditions, corrugator supercilii monitoring reduces the time taken to achieve tracheal intubation compared to adductor pollicis monitoring [90,91]. These latter two studies indicate the use of the orbicularis oculi instead of the corrugator supercilii. In fact, it was the corrugator supercilii that was assessed. With atracurium or rocuronium administered at a suitable dose for tracheal intubation, the fact of systematically waiting for the mean onset time to elapse before starting laryngoscopy ensures the best conditions for intubation.

Question 5: Is the use of muscle relaxants necessary to facilitate interventional procedures and, if so, which ones?

PICO. P = "adult patients receiving muscle relaxants to allow scheduled surgical procedure", I = "muscle relaxants", C = "no muscle relaxants or moderate neuromuscular blockade", O = "surgical field quality score, laparoscopic insufflation pressure".

R5.1 – The use of muscle relaxants is recommended to facilitate interventional procedures in abdominal laparotomy or laparoscopy surgery.

(GRADE 1+) STRONG AGREEMENT

R5.2 – The use of muscle relaxants is probably recommended to facilitate interventional procedures in ENT laser surgery.

(GRADE 2+) STRONG AGREEMENT

Rationale

Most articles published on this topic are to do with abdominal surgery. Three studies involving, respectively, laparotomy prostate surgery [92] laparoscopic cholecystectomies and hysterectomies with a control group receiving placebo or a low dose of muscle relaxant, highlighted an improvement in surgical conditions with intraoperative neuromuscular blockade [93,94]. In laparoscopic surgery, neuromuscular blockade may be useful at the time of pneumoperitoneum establishment to help prevent iatrogenic accidents related to trocar insertion, increase the working space and during aponeurotic closure of trocar incisions. In abdominal

surgery, a deep neuromuscular blockade may improve operating conditions by allowing adequate exposure during laparotomy and, to an even greater extent, during laparoscopy [95–97]. Regarding laryngeal surgery, the results are in favour of a deep neuromuscular blockade with a statistically significant difference regarding exposure of the surgical field (as assessed by the surgeon), intraoperative vocal cord movements and postoperative oral dryness, but with no difference regarding postoperative adverse events [98,99].

No recommendation - Data in the literature are insufficient to be able to establish a recommendation on the required intensity of neuromuscular blockade (moderate *vs.* deep) in abdominal laparotomy or laparoscopy surgery.

Rationale

A few studies have shown the beneficial effect of a deep neuromuscular blockade on surgical conditions from a surgical standpoint. The absolute difference between a deep and a moderate blockade for obtaining good or excellent operating conditions is 25%, i.e. in these studies, one in four patients would have benefited from a deep blockade in terms of operating conditions [100–102]. The question raised by this difference is: which patients should benefit from the deep neuromuscular blockade? So far, the literature has provided no answers to this question. Studies in non-abdominal surgery have concerned spinal surgery but shown no benefits for the deep neuromuscular blockade compared to the moderate blockade [103,104]. However, no trials have shown any difference between the deep blockade and the moderate blockade in terms of intraoperative adverse surgical events or specific morbidity associated with poor exposure. Nevertheless, this lack of difference should be interpreted with caution as the trials all had small sample sizes ($n = 24$ to 102), which were insufficient to reveal any significant difference. It is therefore impossible to make a recommendation on the depth of neuromuscular blockade required to achieve a reduction in intraoperative and postoperative surgical morbidity. The experts only found a few studies focusing on the reduction of pneumoperitoneum pressure according to the depth of neuromuscular blockade: moderate (1 to 2 TOF responses at the adductor pollicis) or deep [1–2 post-tetanic count (PTC) responses at the adductor pollicis]. The randomised study by Madsen et al. ($n = 14$) showed that a deep blockade increased the distance between the umbilical trocar and the promontory by 0.3 cm. This difference is not clinically significant, and the study did not evaluate the risk associated with inserting the first trocar [97]. Three randomised prospective studies were retained. A first randomised study of 67 patients showed a decrease in insufflation pressure for the deepest neuromuscular blockades. The results remain difficult to interpret as the authors compared two levels of deep blockade by monitoring the corrugator supercilii but without a group under moderate blockade, i.e. 1 to 2 TOF responses at the adductor pollicis [100]. In another prospective study including 61 patients, the intra-abdominal pressures required to ensure satisfactory surgical conditions during colorectal surgery were significantly lower in the deep neuromuscular blockade group (9 mmHg) than in the moderate blockade group (12 mmHg, $P < 0.001$) [101]. The third prospective study involved 62 patients undergoing cholecystectomy with an initial insufflation pressure of 8 mmHg. The results showed that insufflation pressure needed to be increased to 12 mmHg in 34% of cases in the moderate neuromuscular blockade group versus 12% in the deep blockade group ($P < 0.05$) [102]. A recent open prospective study showed that the deep neuromuscular blockade allowed a 25% reduction in intra-abdominal pressure compared to an absence of neuromuscular blockade [105].

Question 6: Is intraoperative monitoring of neuromuscular blockade necessary?

PICO. P = "adult patients receiving muscle relaxants to allow a scheduled surgical procedure", I = "intraoperative muscle relaxant injection; neuromuscular blockade monitoring", C = "no monitoring", O = "level of neuromuscular blockade"

R6.1 – Monitoring of neuromuscular blockade intraoperatively is recommended.
(GRADE 1+) STRONG AGREEMENT

R6.2 – The use of train-of-four stimulation of the ulnar nerve at the adductor pollicis is probably recommended to monitor intraoperative neuromuscular blockade.
(GRADE 2+) STRONG AGREEMENT

Rationale

The SFAR recommends intraoperative monitoring of neuromuscular blockade throughout anaesthesia when a muscle relaxant is administered. This recommendation applies both in the operating theatre and the post-anaesthesia care unit. Monitoring the neuromuscular blockade with a nerve stimulator is more accurate than clinical assessment [106]. It is recommended to stimulate the ulnar nerve on the wrist with a visual or tactile evaluation of contraction of the adductor pollicis, given the ease of access and the possibility of quantifying the response in this muscle [107]. The gold standard for intraoperative stimulation remains the evaluation of the adductor pollicis response to train-of-four (TOF) stimulation at the ulnar nerve. The presence of one to two responses after TOF stimulation at the adductor pollicis indicates recovery of about 10% of initial muscle strength [106]. When a deep neuromuscular blockade of the body's most resistant muscles is indicated (diaphragm, abdominal wall muscles), it is recommended to wait until the four responses to TOF stimulation at the adductor pollicis have disappeared and to monitor via post-tetanic count (PTC) stimulation [98,108]. In this case, the presence of one or two responses at the adductor pollicis indicates complete paralysis of the abdominal muscles [108]. TOF stimulation of the facial nerve and visual evaluation of response in the corrugator supercilii offers an alternative to PTC. The neuromuscular blockade profile of the corrugator supercilii is comparable to that of more resistant muscles such as the laryngeal adductor muscles and the diaphragm. Monitoring the orbicularis oculi after stimulation of the facial nerve provides information comparable to that obtained with the adductor pollicis [87]. This may be useful in the absence of intraoperative access to the upper limbs. At the end of the procedure, it is recommended to switch over to adductor pollicis monitoring as soon as possible to quantify recovery [109]. Instrumental acceleromyographic monitoring of the adductor pollicis is more accurate than simple visual or tactile evaluation of muscle contractions [107].

Question 7: What are the strategies for diagnosing and treating residual neuromuscular blockade?

PICO. For question 7.1, P = "adult patients receiving muscle relaxants", I = "muscle relaxants", C = "clinical test for residual neuromuscular blockade, neuromuscular blockade monitoring or absence thereof, muscle sensitivity to neuromuscular blockade",

O = "for residual neuromuscular blockade: frequency, complications related to residual neuromuscular blockade." For questions 7.2 to 7.7, P = "adult patients receiving muscle relaxants", I = "neostigmine, sugammadex", C = "reversal agent or not," O = "quantitative monitoring of neuromuscular blockade, recovery from neuromuscular blockade."

R7.1 – The use of quantitative adductor pollicis monitoring of the neuromuscular blockade is probably recommended for diagnosing a residual neuromuscular blockade and obtaining a ratio of $\geq$ 0.9 for the fourth to first TOF response (T4/T1 ratio) at the adductor pollicis to eliminate the possibility of diagnosing a residual neuromuscular blockade.
(GRADE 2+) STRONG AGREEMENT

Rationale

No clinical test is sensitive enough to detect a residual neuromuscular blockade [110]. Qualitative measurement of the ratio between the fourth and first TOF response (T4/T1) of $\geq$ 0.9 is required to eliminate a diagnosis of residual neuromuscular blockade [111]. Not all muscles are equally sensitive to the effects of muscle relaxants. Monitoring should be carried out on a muscle with high sensitivity to muscle relaxants and slow recovery kinetics. The adductor pollicis meets this profile and is recommended [109]. Only quantitative instrumental monitoring using the T4/T1 ratio measurement at the adductor pollicis with supramaximal stimulation of the ulnar nerve can be used to assess residual neuromuscular blockade [112,113]. The consequences of a residual neuromuscular blockade and the absence of reversal are higher morbidity and mortality within the first twenty-four hours postoperatively [114], a greater risk of critical respiratory events in the recovery room [115,116], a greater risk of postoperative pneumonia [117,118], a greater risk of pharyngeal muscle dysfunction [119], and delayed discharge from the recovery room [120].

R7.2 – After administering a non-depolarising muscle relaxant it is recommended to await spontaneous reversal equal to four muscle responses at the adductor pollicis following TOF stimulation of the ulnar nerve before administering neostigmine.
(GRADE 1+) STRONG AGREEMENT

Rationale

Since neostigmine is a reversible acetylcholinesterase inhibitor, it induces an increase in acetylcholine concentration in the synaptic cleft. Thus, by the law of mass action, non-depolarising muscle relaxants, which are post-synaptic nicotinic acetylcholine receptor antagonists, can unbind from these receptors if two conditions are met:

- the acetylcholine concentration is sufficiently high;
- the concentration of non-depolarising muscle relaxants is sufficiently reduced.

Since the concentration of non-depolarising muscle relaxants is responsible for the degree of neuromuscular blockade, it must have spontaneously reached a certain value to allow the neostigmine to induce an effective reversal, i.e. with a TOF ratio $\geq$ 0.9.

The degree of optimal neuromuscular blockade prior to neostigmine administration was determined in two studies. In the first prospective, randomised study [121], sixty-three patients were divided into four groups based on the number of tactile responses of the adductor pollicis to TOF stimulation prior to administration of neostigmine 70 μg/kg, i.e. one, two, three or four responses. The neuromuscular blockade was induced by cisatracurium. The time taken to achieve a TOF ratio of 0.9 was (minutes, median and ranges) 22.2 (13.9–44.0), 20.2 (6.5–70.5), 17.1 (8.3–46.2) and 16.5 (6.5–143.3) when neostigmine was administered at one, two, three and four responses at the adductor pollicis respectively (not significant). Twenty minutes after neostigmine administration, a TOF ratio of 0.9 was obtained in five out of fourteen patients in Group 1, six out of sixteen patients in Group 2, ten out of sixteen patients in Group 3, and eleven out of fifteen patients in Group 4.

Therefore, the degree of blockade prior to reversal by neostigmine must have spontaneously recovered at least four visual or tactile TOF responses. The second study, of similar methodology, analysed the time it took to obtain a TOF ratio of $>$ 0.9 after rocuronium had been administered [122]. A hundred and sixty patients were divided into eight groups of twenty according to the number of TOF responses at the adductor pollicis (one, two, three and four responses) and according to the anaesthesia maintenance agent (propofol or sevoflurane). Neostigmine was administered at a dose of 70 μg/kg. The time taken to achieve a TOF ratio $>$ 0.9 in the propofol groups (minutes, median and range) was 8.6 (4.7–18.9), 7.5 (3.4–11.2), 5.4 (1.6–8.6) and 4.7 (1.3–7.2) in Groups 1, 2, 3 and 4, respectively ($P < 0.05$ between Group 4 and Groups 1 and 2). In the sevoflurane groups, this time was 26.6 (8.8–75.8), 22.6 (8.3–57.4), 15.6 (7.3–43.9) and 9.7 (5.1–26.4) in Groups 1, 2, 3 and 4 ($P < 0.05$ between Groups 4 and Groups 1 and 2). Recovery times were significantly shorter when anaesthesia was maintained by propofol when compared with sevoflurane ($P < 0.0001$). Ten minutes after administration of neostigmine when four responses at the TOF were obtained, all patients anaesthetised with propofol had a TOF ratio $>$ 0.9 whereas only 11/20 patients (55%) in whom anaesthesia was maintained with sevoflurane. Thus, during maintenance of anaesthesia with propofol, neostigmine 70 μg/kg administered after four tactile adductor pollicis responses to TOF stimulation caused a complete reversal in less than ten minutes. On the other hand, under sevoflurane anaesthesia, reversal was not complete within ten minutes in all patients. All these results suggest that four responses to TOF, corresponding to a measured TOF ratio of $\geq$ 0.2, is the minimum to obtain before administering neostigmine.

R7.3 – It is recommended to administer neostigmine with neuromuscular blockade monitoring at the adductor pollicis, at a dose between 40 and 50 μg/kg adapted to ideal body weight, but not to increase the dose beyond this level, and not to administer it in the absence of residual blockade (Fig. 1).
(GRADE 1+) STRONG AGREEMENT

Rationale

The dose–response relationship of neostigmine administered during a deep blockade, defined by a T1/T0 ratio of 0.01, and during a more moderate blockade, defined by a T1/T0 ratio of 0.1, was established after a neuromuscular blockade by atracurium (T1 is the value of the contraction of the first response to TOF and T0 the value of the first response to TOF before the neuromuscular blockade) [123]. The dose of neostigmine required to obtain a TOF ratio $>$ 0.7, 10 minutes after reversal at T1/T0 = 0.1 (moderate blockade) was 50 ± 7 μg/kg (mean ± SD) and 49 ± 6 μg/kg at T1/T0 = 0.01 (deep blockade) (not significant). It thus appears that, under the study conditions, the dose of neostigmine was in the range of 40 to 50 μg/kg. These results were confirmed when rocuronium was administered [124].

Is there any point in increasing the dose of neostigmine?

Three doses of neostigmine (20, 40 and 80 μg/kg) were administered after randomisation in twenty-seven adult patients when the atracurium-induced blockade had spontaneously returned to a T1/T0 ratio value of between 0.05 and 0.1 [125]. The time it took to obtain a TOF ratio of > 0.7 was (minutes, median and range) 11.3 (9.3–15.7), 8.3 (4.1–13.3), and 5.2 (3.0–14.0) after 20, 40 and 80 μg/kg of neostigmine respectively ($P < 0.04$ between the 20 μg/kg dose and the other two doses). These results suggest that the dose of neostigmine need not be increased due to the occurrence of a ceiling effect. The respiratory effects of neostigmine administered in the absence of residual blockade were demonstrated. In ten healthy volunteers undergoing partial blockade with rocuronium, 30 μg/kg of neostigmine was administered when the TOF ratio spontaneously reached 1.0 [126]. The main objective of this study was to assess the effects of neostigmine on upper airway patency and electromyographic activity of the genioglossus (larynx dilator) muscle. The volunteers were studied four times: before neuromuscular blockade, at TOF ratio 0.5, 1.0 and after neostigmine administration. Administration of neostigmine at TOF ratio = 1.0 caused:

- a significant increase in upper airway closing pressure compared to before the neuromuscular blockade ($p < 0.002$), and when the TOF ratio was 1.0 but before injection of neostigmine ($P < 0.02$);
- a significant reduction in genioglossus electromyographic (EMG) activity in response to an increase in negative upper airway pressure reflecting impaired dilator effect of the genioglossus muscle.

However, no changes in respiratory rate, I/E ratio, tidal volume or train-of-four (TOF) ratio were observed following neostigmine injection under the study conditions. Thus, administering neostigmine after full recovery from the blockade (TOF ratio = 1.0) decreases upper airway patency and reduces laryngeal dilation capacity.

R7.4 – In the event of a very slight residual blockade, it is probably recommended to reduce the neostigmine dose by half.

(GRADE 2+) STRONG AGREEMENT

Rationale

More recently, the concept of reducing the neostigmine dose when the blockade is very shallow has been studied with conflicting results. The effects of three doses of neostigmine (10, 20 and 30 μg/kg) were compared with a placebo to reverse an atracurium-induced blockade when the TOF ratio spontaneously reached 0.4 or 0.6 [127]. A hundred and twenty patients were randomised into eight groups of fifteen. The primary endpoint was the time required to obtain a TOF ratio of 1.0. When the blockade was reversed with a TOF ratio of 0.4, this time was (minutes, median and range): 19 (11–30), 11 (7–15), 9 (9–13) and 6 (4–11) after 0, 10, 20 and 30 μg/kg, respectively. With a TOF ratio of 0.6 before reversal, the time was 15 (8–20), 6 (4–16), 6 (4–14) and 5 (3–7) after 0, 10, 20 and 30 μg/kg, respectively. For example, the dose of neostigmine required to obtain a TOF ratio equal to 1.0 in less than 10 minutes was 25 ± 11 μg/kg and 24 ± 13 μg/kg for neostigmine administered after the TOF ratio had reached 0.4 and 0.6, respectively. These results confirm that the neostigmine dose can be reduced to reverse a very shallow blockade.

In a recent study, three doses of neostigmine (10, 20 and 40 μg/kg) were compared to a placebo when the blockade induced by cisatracurium or rocuronium was spontaneously reversed, reaching 0.5 TOF ratio (i.e. very shallow blockade) [128]. One hundred and twelve patients were included (with fifteen lost to follow-up), i.e. twelve patients per dose of neostigmine. The primary endpoint was the time from injection of neostigmine or placebo to 1.0 TOF ratio. For cisatracurium, the time to reach 1.0 TOF ratio (minutes, median and range) was 16.8 (7.8–29.5), 10.0 (5.0–14.2), 6.5 (4.5–12.6) and 4.3 (2.8–5.3) after 0, 10, 20 and 40 μg/kg of neostigmine, respectively. For rocuronium, this time was 17.5 (7.9–37.5), 6.1 (4.8–27.8), 6.6 (4.3–13.8) and 3.8 (1.5–6.5) after 0, 10, 20 and 40 μg/kg of neostigmine, respectively. Ten minutes after neostigmine administration, the percentage of patients with 1.0 TOF ratio after cisatracurium was 15, 50, 83 and 100% (dose: 0, 10, 20 and 40 μg/kg) and after rocuronium it was 17, 64, 83 and 100% (dose: 0, 10, 20 and 40 μg/kg). These results show that it would be pointless to reduce the neostigmine dose and that the best dose therefore remains 40 μg/kg. However, administering neostigmine at doses that are too high to reverse a very slight residual blockade is not exempt from side effects on neuromuscular transmission. In a study on sixty patients, two doses of neostigmine (20 and 40 μg/kg) were administered one, two, three or four hours after injecting a single dose of vecuronium [129]. In the forty patients receiving neostigmine 40 μg/kg, the TOF ratio had increased in thirty-two patients and decreased in eight of them. These patients had received neostigmine more than two hours after vecuronium and all had a TOF ratio > 0.9 prior to reversal. The decrease in TOF ratio lasted 17.4 to 52.6 minutes. No effects were observed with the 20 μg/kg dose. Neostigmine 40 μg/kg administered whereas the vecuronium-induced blockade has spontaneously reversed (TOF ratio > 0.9) may impair neuromuscular transmission and induce TOF fade.

R7.5 – It is recommended to pursue quantitative monitoring of neuromuscular blockade after administration of neostigmine until a TOF ratio of ≥ 0.9 has been obtained (Fig. 1).

(GRADE 1+) STRONG AGREEMENT

Rationale

The deeper degree of the neuromuscular blockade at the time of reversal, the longer the time between neostigmine administration and complete reversal (i.e. TOF ratio ≥ 0.9). This time ranges from 10 to 30 minutes [121]. After neostigmine administration it is therefore necessary to check the degree of recovery by monitoring the neuromuscular blockade.

R7.6 – It is recommended to adjust the dose of sugammadex according to ideal bodyweight and the intensity of neuromuscular blockade induced by rocuronium (Fig. 2).

(GRADE 1+) STRONG AGREEMENT

R7.7 – After administering sugammadex it is probably recommended to pursue quantitative monitoring of the neuromuscular blockade to detect a possible increase in neuromuscular blockade (Fig. 2).

(GRADE 2+) STRONG AGREEMENT

Rationale

Sugammadex is a gamma cyclodextrin capable of encapsulating steroidal neuromuscular blocking agents specifically (rocuronium and vecuronium). A single sugammadex molecule can only encapsulate one molecule of muscle relaxant. Thus, the higher

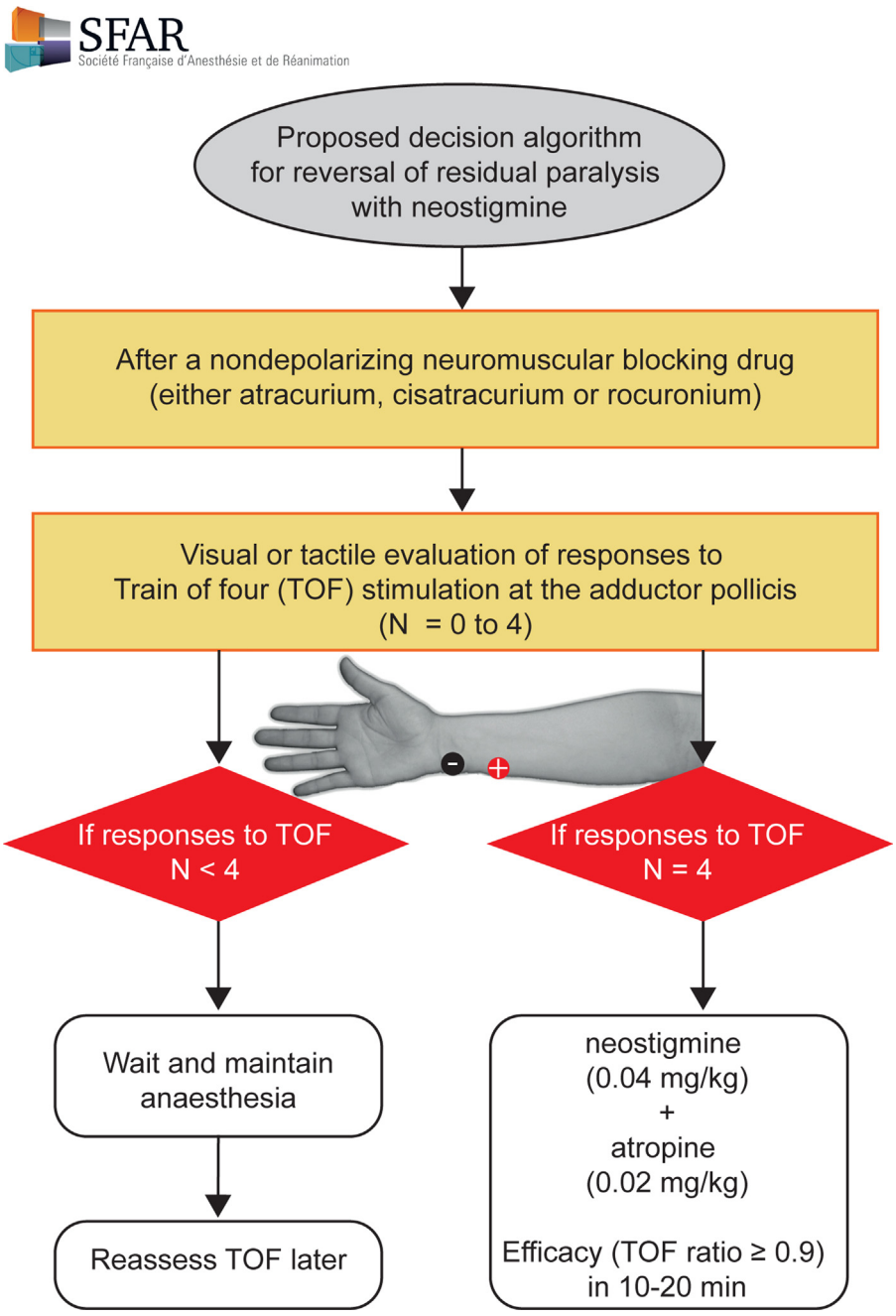


Fig. 1. Decision algorithm for pharmacological non-depolarising neuromuscular blocking drug reversal using neostigmine.
Adapted with permission from Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. Anesthesiology 2010;112:1013–22.

the concentration of steroid muscle relaxant, and therefore the deeper the blockade, the greater the amount of sugammadex that must be administered to reverse the neuromuscular blockade. This simple concept is sufficient to explain the fact that the dose of sugammadex can only be determined after quantifying the neuromuscular blockade. Monitoring is therefore essential. The dose of sugammadex required for reversal was determined for four degrees of blockade:

- very moderate blockade (0.5 TOF ratio): a sugammadex dose of 0.22 mg/kg provided a TOF ratio > 0.9 in less than five minutes in 95% of patients [130];
- moderate blockade (reappearance of two or four visual or tactile adductor pollicis responses to TOF stimulation at the adductor pollicis):
  - when administered on reappearance of four responses to TOF stimulation, 1.0 mg/kg sugammadex reversed a rocuronium-induced neuromuscular blockade in less than five minutes. A dose of 0.5 mg/kg was also effective but slower (ten minutes) [131],
  - when administered on reappearance of two TOF responses, a sugammadex dose of at least 2.0 mg/kg reversed a rocuronium-induced blockade in less than five minutes [132,133];
- deep blockade, i.e. one to two responses to the PTC: to reverse deep rocuronium-induced blockade following a dose of 0.6 or 1.2 mg/kg in less than five minutes, a sugammadex dose of at least 4.0 mg/kg was required [134];
- very deep blockade: to reverse a very deep blockade (three and fifteen minutes after high doses of 1.0 or 1.2 mg/kg rocuronium)

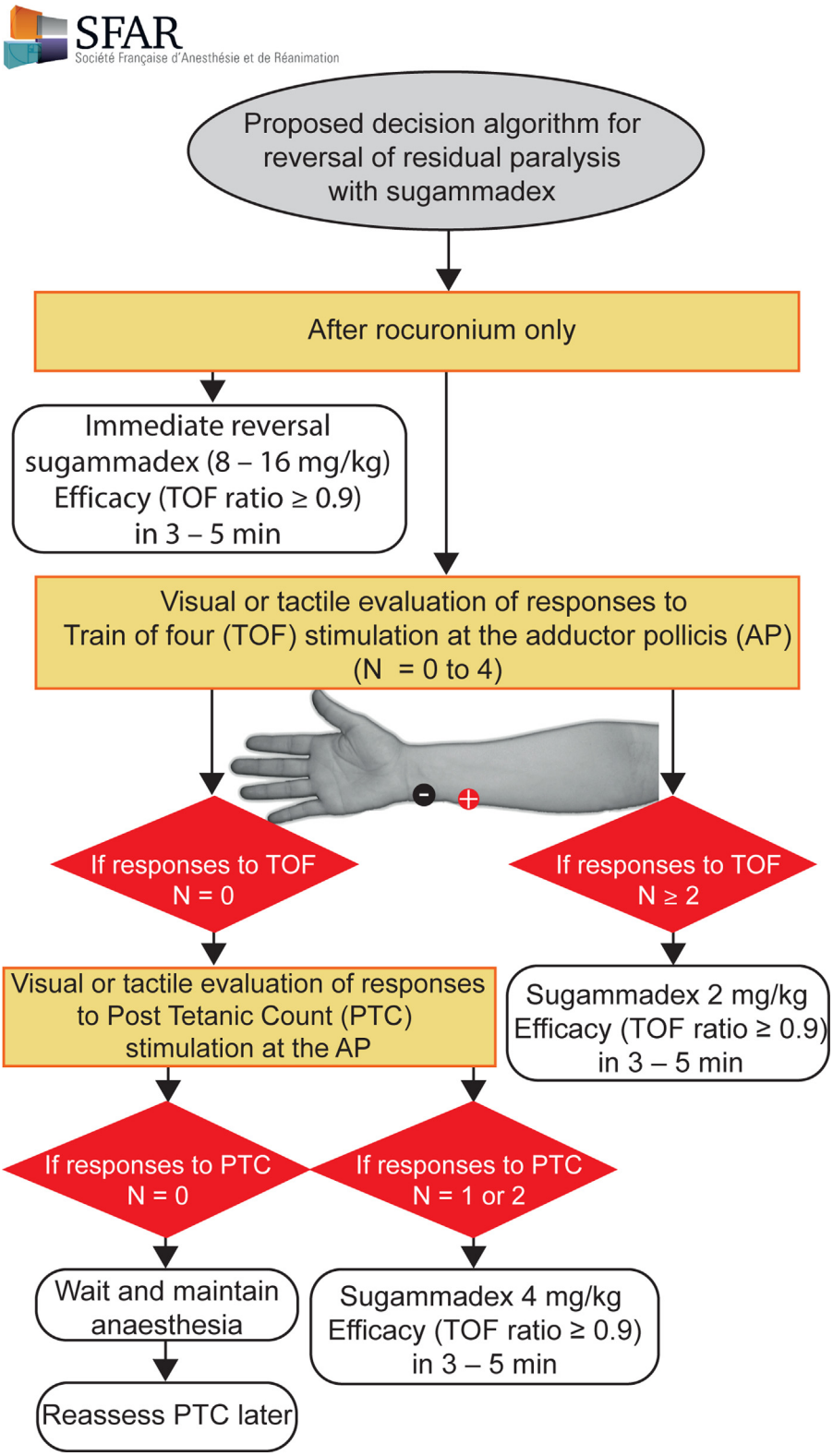


Fig. 2. Decision algorithm for pharmacological non-depolarising neuromuscular blocking drug reversal using sugammadex.
Adapted with permission from Plaud B, Debaene B, Donati F, Marty J. Residual paralysis after emergence from anesthesia. Anesthesiology 2010;112:1013–22.

in less than five minutes, a sugammadex dose of at least 8.0 mg/kg was required [135–137].

An inadequate dose of sugammadex may be the cause of the phenomenon of recurarisation [138]. Thus, the sugammadex dose must be adjusted to the degree of blockade at the time of reversal. Monitoring remains crucial to adjust the sugammadex dose and should be continued after sugammadex administration to identify the potential occurrence of recurarisation [138]. The efficacy of sugammadex is decreased in elderly patients [139] and patients with severe renal failure (creatinine clearance < 30 mL/min) [140], especially in the case of deep blockade reversal (one to two responses to PTC).

Question 8: What are the indications and precautions for use of both muscle relaxants and reversal agents in special populations?

Patients requiring electroconvulsive therapy

PICO. P = "adult patients receiving muscle relaxants for electroconvulsive therapy", I = "muscle relaxants (muscle relaxant type: suxamethonium, rocuronium)", C = "muscle relaxant type", O = "reduction of complications related to generalised convulsion, duration of action according to different dosages".

R8.1 – It is probably recommended to administer a short-acting muscle relaxant for electroconvulsive therapy.
(GRADE 2+) STRONG AGREEMENT

Rationale

The rationale for using muscle relaxants in this setting is to prevent the motor consequences of generalised convulsions such as tongue biting, falls, dislocations and fractures. The specifications are for a fast-acting muscle relaxant that produces brief muscle relaxation during seizures. A systematic review recommends first-line use of suxamethonium. If there are contraindications, a short-acting non-depolarising muscle relaxant may be proposed [141]. A neuromuscular blockade is necessary during electroconvulsive therapy. Suxamethonium remains the gold standard as a muscle relaxant in the vast majority of cases. If there are formal contraindications, combined rocuronium-sugammadex has been proposed in certain case series [142–144].

Obese patients

PICO. P = "severe obese patient", I = "muscle relaxants and reversal agents", C = "different dosages, muscle relaxants and reversal agents", O = "time to obtain complete reversal defined as T4/T1 ratio $>$ 0.9."

R8.2 – For severe obese patients (BMI $\geq$ 40 kg/m^2) it is probably recommended to administer a short-acting muscle relaxant to facilitate tracheal intubation.
(GRADE 2+) STRONG AGREEMENT

R8.3 – It is probably recommended to administer suxamethonium at a dose of 1.0 mg/kg based on the actual body weight of the obese patient.
(GRADE 2+) STRONG AGREEMENT

Rationale

Suxamethonium provides excellent intubating conditions for obese patients when administered at a dose of 1.0 mg/kg adapted to the patient's actual bodyweight [145]. This gives a maximum blockade with high-quality reproducible intubating conditions. Laryngoscope insertion without resistance is facilitated, and the vocal cords are open and motionless. The use of suxamethonium with appropriate dosages calculated for ideal body mass or lean body mass may be associated with poor intubation conditions, resulting in resistance to the introduction of the laryngoscope and movement of the diaphragm and/or lower limbs during tracheal tube positioning.

R8.4 – The experts suggest administration of a non-depolarising muscle relaxant at a dose based on the lean bodyweight of the obese patient.
EXPERT OPINION

Rationale

Non-depolarising muscle relaxants and reversal agents are water-soluble drugs that are distributed in lean mass and extracellular volumes. As a result, apart from suxamethonium, their dose should be calculated based on lean bodyweight, which is higher in obese subjects than in subjects with a normal mass (Janmahasatian formula) [146].

No recommendation - There are insufficient data for any recommendations to be made concerning the interest of a deep blockade for laparoscopic surgery in obese patients.

Rationale

In laparoscopic surgery, compared to a strategy without a muscle relaxant, the neuromuscular blockade leads to improved visibility within the operating field, absence of movement and increased safety of the surgical procedure [94,105]. The depth of blockade remains an unresolved issue. The interest of a deep blockade defined by a PTC of one to two responses, compared to a moderate blockade or TOF stimulation involving two responses, has not been demonstrated as yet. Only one study reported a reduction in intra-abdominal pressure with better operating conditions in patients undergoing laparoscopic colectomy [101]. Another study reported marginally better operability, approaching significance in patients undergoing a cholecystectomy [95]. These studies involved mostly non-obese patients. As no studies have been performed in the obese subjects, no conclusions can be drawn regarding the interest of a deep blockade for laparoscopic surgery in obese patients.

R8.5 – The use of sugammadex adjusted to ideal bodyweight in severe obese patients (BMI $\geq$ 40 kg/m^2) is probably recommended given the increased recovery time and the risk of reappearance of the neuromuscular blockade with neostigmine.
(GRADE 2+) STRONG AGREEMENT

Rationale

With steroid muscle relaxants, administration of neostigmine based on actual bodyweight at a dose of 0.04 mg/kg in combination with atropine 0.02 mg/kg is associated with a longer recovery time in obese subjects compared with non-obese subjects [147]. Sugammadex allows faster reversal than neostigmine [148]. Although the marketing authorisation states that the dose of sugammadex must be adapted to actual bodyweight, reversal of a partial blockade with two responses to TOF was obtained as quickly with a dose of 2.0 mg/kg calculated on the basis of ideal body mass (height in cm minus 110 in women and height in cm minus 100 in men) plus 40% (corrected weight) [149]. In the case of a deep blockade defined by the absence of response to TOF stimulation, the dosage should be increased to 4.0 mg/kg. In this case, adjusting the dosage to ideal bodyweight leads to reversal of the neuromuscular blockade in just over four minutes [150].

Children

R8.6 – Other than situations for which rapid-sequence induction or the use of a depolarising muscle relaxant are indicated, the use of a non-depolarising muscle relaxant is probably recommended to improve intubating conditions during anaesthesia in children by intravenous induction.
(GRADE 2+) STRONG AGREEMENT

Rationale

The SFAR Consensus Conference drawn up in 1999 did not recommend the use of muscle relaxants in children, whether induction is inhaled or intravenous. In fact, in France it is common not to use a muscle relaxant in children [151], and numerous hypnotic/opioid combinations have been reported [152]. However, in the context of intravenous induction, a meta-analysis of randomised studies in children reports improved intubation conditions when muscle relaxants are used [153–160]. In addition, the doses of opioid or hypnotics that allow tracheal intubation without a muscle relaxant are high and have haemodynamic effects that cannot be overlooked [156,158,161]. These results support those of a French cohort study [162]. In reference to the December 2017 ANSM alert on suxamethonium, depolarising muscle relaxants should not be used for intravenous induction, which is not part of a rapid-sequence induction [7]. During inhaled induction, non-use of a muscle relaxant in children is a very common practice in France (92%) [151]. In this context, the duration of exposure to sevoflurane, its concentration, the agent(s) associated with the drug (opioid-propofol) affect the quality of intubating conditions but may also affect haemodynamic parameters [152,163–165]. In all cases, achieving sufficient depth of anaesthesia and obtaining apnoea are the key conditions for success with this technique [166]. However, a muscle relaxant may be used during inhaled induction, especially in infants, for whom a prospective randomised study as well as a large-scale quality assurance study noted benefits associated with the inclusion of a muscle relaxant as regards intubating conditions and respiratory events [86,167]. These data allow the use of a muscle relaxant during inhaled induction in children and militate in favour of studies evaluating circumstances in which the use of muscle relaxants might prove beneficial. These benefits must be considered in the light of low and little-known allergic risk [10,168] and of full mastery by the anaesthetist over neuromuscular blockade and reversal in children.

R8.7 – In rapid-sequence induction, use of a rapid-onset muscle relaxant is recommended in children.

(GRADE 1+) STRONG AGREEMENT

R8.8 – In conventional rapid-sequence induction, it is probably recommended that suxamethonium be given as a first-line drug for rapid-sequence induction in children. Where suxamethonium is contraindicated, use of rocuronium is probably recommended.

(GRADE 2+) STRONG AGREEMENT

Rationale for 8.7 and 8.8

As in adults, it is recommended to limit the time between loss of consciousness and protection of the upper airways through intubation [169,170]. This time must be kept short since the duration of apnoea without hypoxemia is shorter in younger children [171]. Use of a muscle relaxant to improve intubation conditions, a muscle relaxant-free intubation technique or inhaled induction techniques are not recommended. Regarding fast-acting muscle relaxants, suxamethonium remains the expert choice. Age-appropriate doses of suxamethonium have been determined ($<$ 1 month: 1.8 mg/kg, $>$ 1 month and $<$ 1 year: 2.0 mg/kg, $>$ 1 year and $<$ 10 years: 1.2 mg/kg, $>$ 10 years: 1.0 mg/kg). Rocuronium at a dose higher than 0.9 mg/kg [172] may offer an alternative to suxamethonium, however, in 2018 sugammadex had not yet been granted marketing approval for children aged under two. The choice between suxamethonium and rocuronium will thus be based on the desired duration of neuromuscular blockade, the anticipated difficulties of intubation, and the presence and/or risk of ignoring underlying myopathy. The muscle relaxant most often compared to suxamethonium in the literature is rocuronium due to its rapid-onset of action and the intubating conditions it offers [173]. The dosage is 0.6 to 0.9 mg/kg [172].

A retrospective cohort study identified no difference in incidence of complications between suxamethonium and non-depolarising muscle relaxants in terms of respiratory risk and difficult intubations [174]. In the latest Cochrane review, which assesses intubating conditions with rocuronium and suxamethonium, suxamethonium provides intubating conditions equivalent to or better than those obtained with rocuronium despite numerous biases in the various studies [8]. This review therefore concludes that suxamethonium should continue to be preferred (especially since its duration of action is shorter) and that rocuronium should only be used where suxamethonium is contraindicated [8,175]. Contraindications to suxamethonium include risk of malignant hyperthermia, muscle diseases with risk of rhabdomyolysis, hyperkalaemia, allergy and situations involving risk of hyperkalaemia [174]. Sugammadex has demonstrated its value in reversing the effects of rocuronium [176,177]. Indeed, a recent meta-analysis by Won et al. showed that sugammadex shortens mean time to achievement of $\geq$ 0.9 TOF ratio, with an extubation time comparable to neostigmine or placebo [176]. The conclusions of the studies regarding risk of anaphylaxis are contradictory. The study by Reddy et al. shows a similar risk of anaphylaxis for suxamethonium and rocuronium [13]. Reitter et al. found a higher risk with suxamethonium in the results cited in the study appendix [178]. This risk may be lower with atracurium and cisatracurium, but it is present nonetheless [13,179]. Moreover, the risk of anaphylaxis with sugammadex does not appear to be negligible [180,181].

No recommendation - There is insufficient data on which to base any recommendations regarding the administration of a muscle relaxant in children to facilitate face mask ventilation, the insertion of supraglottic devices and management of related complications and surgical procedures and facilitate surgery or regarding the value of neuromuscular blockade monitoring for intraoperative tracheal intubation or the diagnosis and treatment of a residual neuromuscular blockade.

Rationale

In paediatric anaesthesia, the frequency of residual neuromuscular blockade is estimated at 28% in children receiving a muscle relaxant and monitoring is therefore warranted [182]. There are no studies evaluating the occurrence of adverse events depending on whether a reversal agent is given. Similarly, there are no studies comparing the incidence of residual neuromuscular blockade based on age or the application of a neuromuscular blockade monitoring strategy.

Neuromuscular diseases

PICO: P = "patients with neuromuscular diseases", I = "administration of different types of muscle relaxant", C = "patients with or without neuromuscular disease", O = "degree of neuromuscular blockade, side effects, residual neuromuscular blockade, reversal agents".

R8.9 – The use of suxamethonium is not recommended in cases of primary muscle damage (myopathies) or up-regulation of nicotinic acetylcholine receptors at the motor end plate (chronic motor deficit).

(GRADE 1−) STRONG AGREEMENT

Rationale

Suxamethonium is contraindicated in both these situations. In specific muscle disorders (myopathy, myotonia), it induces generalised contraction with rhabdomyolysis [183]. In the event of impairment of the nicotinic acetylcholine receptors (nAChRs) at the motor end plate through up-regulation (chronic damage of motoneurons, extensive and deep burns, prolonged critical illness), suxamethonium can cause life-threatening hyperkalaemia a few days after constitution of the neurological and/or muscle lesions, and over an extended period of time [183–185].

R8.10 – Monitoring of neuromuscular blockade is probably recommended following muscle relaxant use in patients with neuromuscular disease.

(GRADE 2+) STRONG AGREEMENT

Rationale

In cases of down-regulation of nAchRs (myasthenia), muscle relaxants are not contraindicated but significant pharmacodynamic changes have been reported. With suxamethonium, resistance is observed (decreased potency and need to increase the dose to achieve the same effect) [186,187]. For non-depolarising muscle relaxants, there is an increase in sensitivity and in duration of action, with reduced intraoperative dose requirement. A 50–75% reduction in the recommended dose is common with atracurium and cisatracurium [188,189]. This reduction in dose requirement correlates with the severity of myasthenia. Neuromuscular blockade monitoring is recommended to avoid overdosing. Evaluation in myasthenic patients of the TOF ratio by EMG in the hypothenar hand muscles prior to muscle relaxant administration predicts sensitivity to non-depolarising muscle relaxants. If the TOF ratio is less than 0.9 before the neuromuscular blockade, sensitivity to muscle relaxants is greater and the injected doses must be lower than in myasthenic subjects with a ratio greater than 0.9 [190]. In the case of primary muscle damage, there is a very significant increase in sensitivity to rocuronium (reduced dose requirement). A comparative study showed that after a dose of 0.6 mg/kg of rocuronium, onset and recovery times were significantly longer for Duchenne muscular dystrophy patients compared to controls [191]. In cases of up-regulation of nAchRs, sensitivity to non-depolarising muscle relaxants is reduced and higher doses are required to achieve the same effect [192]. The small populations in the various studies warrant GRADE 2 classification.

R8.11 – Administration of sugammadex is probably recommended for reversal of a residual neuromuscular blockade following the use of a steroidal muscle relaxant in patients with neuromuscular disease.

(GRADE 2+) STRONG AGREEMENT

Rationale

The risks of residual neuromuscular blockade are increased in neuromuscular disease. In myasthenia patients, neostigmine may interfere with long-term treatment. In primary muscle damage, neostigmine and atropine are difficult to deal with due to drying of secretions (atropine), potential rhythm and conduction disorders (both), central effects (atropine), slow response and effects on muscle action potential (neostigmine). Case series have described the use of sugammadex as a reversal agent for rocuronium in patients with neuromuscular disease [193,194]. The results are comparable with those observed in clinical trials conducted in subjects without neuromuscular disease (see R-7.2) regarding efficacy and time to onset of action. The small sample sizes of patients in the different studies warrant GRADE 2 classification.

Renal/hepatic failure, elderly subjects

R8.12 – The use of a benzylisoquinoline muscle relaxant (atracurium/cisatracurium) is probably recommended in cases of renal/hepatic failure.

(GRADE 2+) STRONG AGREEMENT

Rationale

In this setting, the pharmacodynamics of muscle relaxants excreted by kidney or liver are modified and their elimination is delayed. This may result in extended duration of action of these agents, particularly with repeated injections or continuous infusion [195]. In addition, interindividual response variability is greater in these populations, resulting in increased difficulty in dealing with these agents. Rocuronium is mainly eliminated in urine and bile [196] and its clearance is thus reduced in renal failure patients [197] and cirrhotic patients, in whom there is wide variability in the duration of action of repeated injections [198]. The pharmacokinetics and pharmacodynamics of atracurium, roughly half of which is eliminated by organ-independent reactions (Hofmann reaction and ester hydrolysis) and half by metabolism or excretion [199], are similar in subjects with and without kidney and liver failure [200,201]. On the other hand, its active metabolite, laudanosine, accumulates in patients in renal failure but does not reach concentrations causing adverse effects, even after infusion for up to 72 hours [202]. Cisatracurium, one of the ten isomers of atracurium, elimination of which is overwhelmingly non-enzymatic [203], also has similar pharmacokinetic and pharmacodynamic profiles in patients with and without renal and hepatic failure [204]. Since this agent is more potent than atracurium, the doses, and hence the amounts of laudanosine generated, are significantly lower.

R8.13 – It is recommended not to modify the initial dose in renal/hepatic failure patients, irrespective of the type of muscle relaxant used.

(GRADE 1+) STRONG AGREEMENT

Rationale

While the duration of action of a single dose of rocuronium is extended in renal failure patients and in the elderly, the time to onset of action remains unchanged [205]. In cirrhotic patients, the efficacy of the initial dose of rocuronium is reduced since the increase in distribution volume results in a lower concentration [198]. However, this effect is particularly remarkable at low doses and is no longer clinically noticeable at intubation doses [198]. The same is true of atracurium [206] and cisatracurium [207] in renal/hepatic failure. Consequently, to ensure effective concentrations of muscle relaxants during intubation, it is necessary and sufficient to administer the usual dose in both renal and hepatic failure patients and cirrhotic patients.

R8.14 – When using sugammadex in cases of renal failure, it is probably recommended to administer it at the usual dose.

(GRADE 2+) STRONG AGREEMENT

Rationale

Sugammadex is eliminated in urine and thus accumulates in renal failure patients [197]. However, clinical studies have shown

that the efficacy of sugammadex is maintained in renal failure patients at the same doses as in subjects with normal renal function, without any signs of recurarisation [208]. Sugammadex may be removed by dialysis, as may sugammadex-rocuronium complex [209].

No recommendation - There is insufficient data in the literature to establish a recommendation concerning the use of muscle relaxants in the elderly.

Disclosure of interest

Christophe Baillard, Bertrand Debaene, Thomas Fuchs-Buder, Gilles Lebuffe, Benoît Plaud, Claude Meistelman, Julien Raft, Karem Slim, Didier Sirieix report personal fees from Merck Sharp & Dohme™ France.

Jean-Louis Bourgain, Gaëlle Bouroche, Laetitia Desplanque, Jean-Michel Devys, Dominique Fletcher, Cyrus Motamed, Frédérique Servin, Lionel Velly, Franck Verdonk declare that they have no competing interest.

References

[1] Indication de la curarisation en anesthésie. Ann Fr Anesth Reanim 2000;19:34–7.
[2] Debaene B, Bruder N, Chollet-Rivier M. Induction of anaesthesia: intravenous agents, inhaled agents, opioids, muscle relaxants; monitoring. Ann Fr Anesth Reanim 2003;22:53s–9s.
[3] Langeron O, Bourgain JL, Francon D, Amour J, Baillard C, Bouroche G, et al. Difficult intubation and extubation in adult anaesthesia. Anaesth Crit Care Pain Med 2018;37:639–51.
[4] Vivien B, Adnet F, Bounes V, Chéron G, Combes X, David JS, et al. Sedation and analgesia in emergency structure. Reactualization 2010 of the Conference of Experts of SFAR of 1999. Ann Fr Anesth Reanim 2012;31:391–404.
[5] Sauder P, Andreoletti M, Cambonie G, Capellier G, Feissel M, Gall O, et al. Sedation and analgesia in intensive care (with the exception of new-born babies). French Society of Anesthesia and Resuscitation. French-speaking Resuscitation Society. Ann Fr Anesth Reanim 2008;27:541–51.
[6] Société française d'anesthésie et réanimation (SFAR), Société française d'allergologie (SFA). Reducing the risk of anaphylaxis during anaesthesia. Short text. Société française d'anesthésie et réanimation. Société française d'allergologie. Ann Fr Anesth Reanim 2011;30:212–22.
[7] Produits injectables à base de suxaméthonium: restriction d'indications – Lettre aux professionnels de santé. ANSM. https://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Produits-injectables-a-base-de-suxamethonium-restriction-d-indications-Lettre-aux-professionnels-de-sante. [Last access 08/01/2020].
[8] Tran DTT, Newton EK, Mount VAH, Lee JS, Welles GA, Perry JJ. Rocuronium versus succinylcholine for rapid sequence induction. Cochrane Database Syst Rev)2015;(10). http://dx.doi.org/10.1002/14651858.CD002788.pub3 [Art. No.: CD002788].
[9] Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM, GERAP. Hyerpsensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). Minerva Anestesiol 2012;78:868–78.
[10] Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E, Groupe d'Études des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. J Allergy Clin Immunol 2011;128:366–73.
[11] Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway. Anesthesiology 2005;102:897–903.
[12] Sadleir PHM, Clarke RC, Bunning DL, Platt PR. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in western Australia from 2002 to 2011. Br J Anaesth 2013;110:981–7.
[13] Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. Anesthesiology 2015;122:39–45.
[14] Combes X, Le Roux B, Suen P, Dumerat M, Motamed C, Sauvat S, et al. Unanticipated difficult airway in anesthetized patients: prospective validation of a management algorithm. Anesthesiology 2004;100:1146–50.
[15] Kheterpal S, Healy D, Aziz MF, Shanks AM, Freundlich RE, Linton F, et al. Incidence, predictors, and outcome of difficult mask ventilation combined with difficult laryngoscopy: a report from the multicenter perioperative outcomes group. Anesthesiology 2013;119:1360–9.
[16] Heier T, Feiner JR, Lin J, Brown R, Caldwell JE. Hemoglobin desaturation after succinylcholine-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. Anesthesiology 2001;94:754–9.
[17] Stefanutto TB, Feiner J, Krombach J, Brown R, Caldwell JE. Hemoglobin desaturation after propofol/remifentanil-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. Anesth Analg 2012;114:980–6.
[18] Woods A, Grant S, Davidson A. Duration of apnoea with two different intubating doses of remifentanil. Eur J Anaesthesiol 1999;16:634–7.
[19] McNeil IA, Culbert B, Russell I. Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2 micrograms kg-1 or 4 micrograms kg-1. Br J Anaesth 2000;85:623–5.
[20] Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology 1997;86:613–9.
[21] Nieuwenhuijs D, Sarton E, Teppema LJ, Kruyt E, Olievier I, van Kleef J, et al. Respiratory sites of action of propofol: absence of depression of peripheral chemoreflex loop by low-dose propofol. Anesthesiology 2001;95:889–95.
[22] Dhonneur G, Kirov K, Slavov V, Duvaldestin P. Effects of an intubating dose of succinylcholine and rocuronium on the larynx and diaphragm: an electromyographic study in humans. Anesthesiology 1999;90:951–5.
[23] Sørensen MK, Bretlau C, Gätke MR, Sørensen AM, Rasmussen LS. Rapid sequence induction and intubation with rocuronium-sugammadex compared with succinylcholine: a randomized trial. Br J Anaesth 2012;108:682–9.
[24] Naguib M, Samarkandi AH, Abdullah K, Riad W, Alharby SW. Succinylcholine dosage and apnea-induced hemoglobin desaturation in patients. Anesthesiology 2005;102:35–40.
[25] Bisschops MM, Holleman C, Huitink JM. Can sugammadex save a patient in a simulated 'cannot intubate, cannot ventilate' situation? Anaesthesia 2010;65:936–41.
[26] Kyle BC, Gaylard D, Riley RH. A persistent 'can't intubate, can't oxygenate' crisis despite rocuronium reversal with sugammadex. Anaesth Intensive Care 2012;40:344–6.
[27] Bennett JA, Abrams JT, Van Riper DF, Horrow JC. Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology 1997;87:1070–4.
[28] Nakada J, Nishira M, Hosoda R, Funaki K, Takahashi S, Matsura T, et al. Priming with rocuronium or vecuronium prevents remifentanil-mediated muscle rigidity and difficult ventilation. J Anesth 2009;23:323–8.
[29] Andel H, Klune G, Andel D, Felfernig M, Donner A, Schramm W, et al. Propofol without muscle relaxants for conventional or fiberoptic nasotracheal intubation: a dose-finding study. Anesth Analg 2000;91:458–61.
[30] Goodwin MW, Pandit JJ, Hames K, Popat M, Yentis SM. The effect of neuromuscular blockade on the efficiency of mask ventilation of the lungs. Anaesthesia 2003;58:60–3.
[31] Ikeda A, Isono S, Sato Y, Yogo H, Sato J, Ishikawa T, et al. Effects of muscle relaxants on mask ventilation in anesthetized persons with normal upper airway anatomy. Anesthesiology 2012;117:487–93.
[32] Sachdeva R, Kannan TR, Mendonca C, Patteril M. Evaluation of changes in tidal volume during mask ventilation following administration of neuromuscular blocking drugs. Anaesthesia 2014;69:826–31.
[33] Joffe AM, Ramaiah R, Donahue E, Galgon RE, Thilen SR, Spiekerman CF, et al. Ventilation by mask before and after the administration of neuromuscular blockade: a pragmatic non-inferiority trial. BMC Anesthesiol 2015;15:134.
[34] Warters RD, Szabo TA, Spinale FG, DeSantis SM, Reves JG. The effect of neuromuscular blockade on mask ventilation. Anaesthesia 2011;66:163–7.
[35] Amathieu R, Combes X, Abdi W, Housseini LE, Rezzoug A, Dinca A, et al. An algorithm for difficult airway management, modified for modern optical devices (Airtraq laryngoscope; LMA CTrach): a 2-year prospective validation in patients for elective abdominal, gynecologic, and thyroid surgery. Anesthesiology 2011;114:25–33.
[36] Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia 1984;39:1105–11.
[37] Yentis SM, Lee DJ. Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anaesthesia 1998;11:1041–4.
[38] Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007;7:789–808.
[39] Alexander R, Olufolabi AJ, Booth J, El-Moalem HE, Glass PS. Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. Anaesthesia 1999;11:1037–40.
[40] Barclay K, Eggers K, Asai T. Low-dose rocuronium improves conditions for tracheal intubation after induction of anaesthesia with propofol and alfentanil. Br J Anaesth 1997;78:92–4.
[41] Beck GN, Masterson GR, Richards J, Bunting P. Comparison of intubation following propofol and alfentanil with intubation following thiopentone and suxamethonium. Anaesthesia 1993;48:876–80.
[42] Bouvet L, Stoian A, Jacquot-Laperrière S, Allaouchiche B, Chassard D, Boselli E. Laryngeal injuries and intubating conditions with or without muscular relaxation: an equivalence study. Can J Anaesth 2008;55:674–84.
[43] Combes X, Andriamifidy L, Dufresne E, Suen P, Sauvat S, Scherrer E, et al. Comparison of two induction regimens using or not using muscle relaxant: impact on postoperative upper airway discomfort. Br J Anaesth 2007;99:276–81.
[44] Dominici L, Gondret R, Dubos S, Crevot O, Delingé P. Intubation in otorhinolaryngologic surgery: propofol versus propofol-suxamethonium. Ann Fr Anesth Reanim 1990;9:110–4.
[45] Gulhas N, Topal S, Erdogan Kayhan G, Yucel A, Begec Z, Yologlu S, et al. Remifentanil without muscle relaxants for intubation in microlaryngoscopy: a double blind randomised clinical trial. Eur Rev Med Pharmacol Sci 2013;17:1967–73.
[46] Hanna SF, Ahmad F, Pappas AL, Mikat-Stevens M, Jellish WS, Kleinman B, et al. The effect of propofol/remifentanil rapid-induction technique without muscle relaxants on intraocular pressure. J Clin Anesth 2010;22:437–42.

[47] Harsten A, Gillberg L. Intubating conditions provided by propofol and alfentanil – acceptable, but not ideal. Acta Anaesthesiol Scand 1997;41:985–7.
[48] Iamaroon A, Pitimana-aree S, Prechawai C, Anusit J, Somcharoen K, Chaiyaroj O. Endotracheal intubation with thiopental/succinylcholine or sevoflurane-nitrous oxide anesthesia in adults: a comparative study. Anesth Analg 2001;92:523–8.
[49] Isesele T, Amadasun F, Edomwonyi N. Comparison of intubating conditions with propofol suxamethonium versus propofol-lidocaine. J West Afr Coll Surg 2012;2:51–67.
[50] Jiao J, Huang S, Chen Y, Liu H, Xie Y. Comparison of intubation conditions and apnea time after anesthesia induction with propofol/alfentanil combined with or without small doses of succinylcholine. Int J Clin Exp Med 2014;7:393–9.
[51] Kahwaji R, Bevan DR, Bikhazi G, Shanks CA, Fragen RJ, Dyck JB, et al. Dose-ranging study in younger adult and elderly patients of ORG 9487, a new, rapid-onset, short-duration muscle relaxant. Anesth Analg 1997;84:1011–8.
[52] Kirkegaard-Nielsen H, Caldwell JE, Berry PD. Rapid tracheal intubation with rocuronium: a probability approach to determining dose. Anesthesiology 1999;91:131–6.
[53] Kopman AF, Klewicka MM, Neuman GG. Reexamined: the recommended endotracheal intubating dose for nondepolarizing neuromuscular blockers of rapid onset. Anesth Analg 2001;93:954–9.
[54] Lieutaud T, Billard V, Khalaf H, Debaene B. Muscle relaxation and increasing doses of propofol improve intubating conditions. Can J Anaesth 2003;50:121–6.
[55] Lowry DW, Carroll MT, Mirakhur RK, Hayes A, Hughes D, O'Hare R. Comparison of sevoflurane and propofol with rocuronium for modified rapid-sequence induction of anaesthesia. Anaesthesia 1999;54:247–52.
[56] Mencke T, Echternach M, Kleinschmidt S, Barth V, Plinkert PK, Fuchs-Buder T. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. Anesthesiology 2003;98:1049–56.
[57] Mencke T, Jacobs RM, Machmueller S, Sauer M, Heidecke C, Kallert A, et al. Intubating conditions and side effects of propofol, remifentanil and sevoflurane compared with propofol, remifentanil and rocuronium: a randomised, prospective, clinical trial. BMC Anesthesiol 2014;14:39.
[58] Naguib M, Samarkandi A, Riad W, Alharby SW. Optimal dose of succinylcholine revisited. Anesthesiology 2003;99:1045–9.
[59] Naguib M, Samarkandi AH, El-Din ME, Abdullah K, Khaled M, Alharby SW. The dose of succinylcholine required for excellent endotracheal intubating conditions. Anesth Analg 2006;102:151–5.
[60] Nimmo SM, McCann N, Broome IJ, Robb HM. Effectiveness and sequelae of very low-dose suxamethonium for nasal intubation. Br J Anaesth 1995;74:31–4.
[61] Pang L, Zhuang YY, Dong S, Ma HC, Ma HS, Wang YF. Intubation without muscle relaxation for suspension laryngoscopy: a randomized, controlled study. Niger J Clin Pract 2014;17:456–61.
[62] Pino RM, Ali HH, Denman WT, Barrett PS, Schwartz A. A comparison of the intubation conditions between mivacurium and rocuronium during balanced anesthesia. Anesthesiology 1998;88:673–8.
[63] Rousseau JM, Lemardeley P, Giraud D, Lemarié J, Ladagnous JF, Barriot P, et al. Endotracheal intubation under propofol with or without vecuronium. Ann Fr Anesth Reanim 1995;14:261–4.
[64] Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. Anesth Analg 1992;75:788–93.
[65] Schlaich N, Mertzlufft F, Soltész S, Fuchs-Buder T. Remifentanil and propofol without muscle relaxants or with different doses of rocuronium for tracheal intubation in outpatient anaesthesia. Acta Anaesthesiol Scand 2000;44:720–6.
[66] Sivalingam P, Kandasamy R, Dhakshinamoorthi P, Madhavan G. Tracheal intubation without muscle relaxant – a technique using sevoflurane vital capacity induction and alfentanil. Anaesth Intensive Care 2001;29:383–7.
[67] Stevens JB, Vescovo MV, Harris KC, Walker SC, Hickey R. Tracheal intubation using alfentanil and no muscle relaxant: is the choice of hypnotic important? Anesth Analg 1997;84:1222–6.
[68] Striebel HW, Hölzl M, Rieger A, Brummer G. Endotracheal intubation with propofol and fentanyl. Anaesthesist 1995;44:809–17.
[69] Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gätke MR, Wetterslev J. Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103,812 consecutive adult patients recorded in the Danish Anaesthesia Database. Br J Anaesth 2009;103:283–90.
[70] Lundstrøm LH, Duez CHV, Nørskov AK, Rosenstock CV, Thomsen JL, Møller AM, et al. Effects of avoidance or use of neuromuscular blocking agents on outcomes in tracheal intubation: a Cochrane systematic review. Br J Anaesth 2018;120:1381–93.
[71] Chen B, Tan L, Zhang L, Shang Y. Is muscle relaxant necessary in patients undergoing laparoscopic gynecological surgery with a ProSeal LMATM? J Clin Anesth 2013;25:32–5.
[72] Gong Y-H, Yi J, Zhang Q, Xu L. Effect of low dose rocuronium in preventing ventilation leak for flexible laryngeal mask airway during radical mastectomy. Int J Clin Exp Med 2015;8:13616–21.
[73] Aghamohammadi D, Eydi M, Hosseinzadeh H, Amiri Rahimi M, Golzari SE. Assessment of mini-dose succinylcholine effect on facilitating laryngeal mask airway insertion. J Cardiovasc Thorac Res 2013;5:17–21.
[74] Fujiwara A, Komasawa N, Nishihara I, Miyazaki S, Tatsumi S, Nishimura W, et al. Muscle relaxant effects on insertion efficacy of the laryngeal mask ProSeal(®) in anesthetized patients: a prospective randomized controlled trial. J Anesth 2015;29:580–4.
[75] Kong M, Li B, Tian Y. Laryngeal mask airway without muscle relaxant in femoral head replacement in elderly patients. Exp Ther Med 2016;11:65–8.
[76] Yoshino A, Hashimoto Y, Hirashima J, Hakoda T, Yamada R, Uchiyama M. Low-dose succinylcholine facilitates laryngeal mask airway insertion during thiopental anaesthesia. Br J Anaesth 1999;83:279–83.
[77] Saito T, Liu W, Chew STH, Ti LK. Incidence of and risk factors for difficult ventilation *via* a supraglottic airway device in a population of 14,480 patients from South-East Asia. Anaesthesia 2015;70:1079–83.
[78] Sasaki CT, Leder SB, Acton LM, Maune S. Comparison of the glottic closure reflex in traditional "open" versus endoscopic laser supraglottic laryngectomy. Ann Otol Rhinol Laryngol 2006;115:93–6.
[79] Afshan G, Chohan U, Qamar-Ul-Hoda M, Kamal RS. Is there a role of a small dose of propofol in the treatment of laryngeal spasm? Paediatr Anaesth 2002;12:625–8.
[80] Al-alami AA, Zestos MM, Baraka AS. Pediatric laryngospasm: prevention and treatment. Curr Opin Anaesthesiol 2009;22:388–95.
[81] Meistelman C, Plaud B, Donati F. Neuromuscular effects of succinylcholine on the vocal cords and adductor pollicis muscles. Anesth Analg 1991;73:278–82.
[82] Seah TG, Chin NM. Severe laryngospasm without intravenous access – a case report and literature review of the non-intravenous routes of administration of suxamethonium. Singapore Med J 1998;39:328–30.
[83] Warner DO. Intramuscular succinylcholine and laryngospasm. Anesthesiology 2001;95:1039–40.
[84] Rawicz M, Brandom BW, Wolf A. The place of suxamethonium in pediatric anesthesia. Paediatr Anaesth 2009;19:561–70.
[85] Ghimouz A, Lentschener C, Goater P, Borne M, Esteve M. Adducted vocal cords relieved by neuromuscular blocking drug: a cause of impaired mechanical ventilation when using a laryngeal mask airway: two photographically documented cases. J Clin Anesth 2014;26:668–70.
[86] Spaeth JP, Kreeger R, Varughese AM, Wittkugel E. Interventions designed using quality improvement methods reduce the incidence of serious airway events and airway cardiac arrests during pediatric anesthesia. Paediatr Anaesth 2016;26:164–72.
[87] Plaud B, Debaene B, Donati F. The corrugator supercilii, not the orbicularis oculi, reflects rocuronium neuromuscular blockade at the laryngeal adductor muscles. Anesthesiology 2001;95:96–101.
[88] Lee HJ, Kim KS, Jeong JS, Cheong MA, Shim JC. Comparison of the adductor pollicis, orbicularis oculi, and corrugator supercilii as indicators of adequacy of muscle relaxation for tracheal intubation. Br J Anaesth 2009;102:869–74.
[89] Lee HJ, Kim KS, Jeong JS, Shim JC, Oh YN. Comparison of four facial muscles, orbicularis oculi, corrugator supercilii, masseter or mylohyoid, as best predictor of good conditions for intubation: a randomised blinded trial. Eur J Anaesthesiol 2013;30:556–62.
[90] Debaene B, Beaussier M, Meistelman C, Donati F, Lienhart A. Monitoring the onset of neuromuscular block at the orbicularis oculi can predict good intubating conditions during atracurium-induced neuromuscular block. Anesth Analg 1995;80:360–3.
[91] Le Corre F, Plaud B, Benhamou E, Debaene B. Visual estimation of onset time at the orbicularis oculi after five muscle relaxants: application to clinical monitoring of tracheal intubation. Anesth Analg 1999;89:1305–10.
[92] King M, Sujirattanawimol N, Danielson DR, Hall BA, Schroeder DR, Warner DO. Requirements for muscle relaxants during radical retropubic prostatectomy. Anesthesiology 2000;93:1392–7.
[93] Dubois PE, Putz L, Jamart J, Marotta ML, Gourdin M, Donnez O. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: a randomised controlled trial. Eur J Anaesthesiol 2014;31:430–6.
[94] Blobner M, Frick CG, Stauble RB, Feussner H, Schaller SJ, Unterbuchner C, et al. Neuromuscular blockade improves surgical conditions (NISCO). Surg Endosc 2015;29:627–36.
[95] Staehr-Rye AK, Rasmussen LS, Rosenberg J, Juul P, Lindekaer AL, Riber C, et al. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade: a randomized clinical study. Anesth Analg 2014;119:1084–92.
[96] Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. Br J Anaesth 2014;112:498–505.
[97] Madsen MV, Gätke MR, Springborg HH, Rosenberg J, Lund J, Istre O. Optimising abdominal space with deep neuromuscular blockade in gynaecologic laparoscopy – a randomised, blinded crossover study. Acta Anaesthesiol Scand 2015;59:441–7.
[98] Kim HJ, Lee K, Park WK, Lee BR, Joo HM, Koh YW, et al. Deep neuromuscular block improves the surgical conditions for laryngeal microsurgery. Br J Anaesth 2015;115:867–72.
[99] Huh H, Park SJ, Lim HH, Jung KY, Baek SK, Yoon SZ, et al. Optimal anesthetic regimen for ambulatory laser microlaryngeal surgery. Laryngoscope 2017;127:1135–9.
[100] Yoo YC, Kim NY, Shin S, Choi YD, Hong JH, Kim CY, et al. The intraocular pressure under deep versus moderate neuromuscular blockade during low-pressure robot assisted laparoscopic radical prostatectomy in a randomized trial. PloS One 2015;10:e0135412.

[101] Kim MH, Lee KY, Lee KY, Min BS, Yoo YC. Maintaining optimal surgical conditions with low insufflation pressures is possible with deep neuromuscular blockade during laparoscopic colorectal surgery: a prospective, randomized, double-blind, parallel-group clinical trial. Medicine 2016;95:e2920.
[102] Koo BW, Oh AY, Seo KS, Han JW, Han HS, Yoon YS. Randomized clinical trial of moderate versus deep neuromuscular block for low-pressure pneumoperitoneum during laparoscopic cholecystectomy. World J Surg 2016;40:2898–903.
[103] Li YL, Liu YL, Xu CM, Lv XH, Wan ZH. The effects of neuromuscular blockade on operating conditions during general anesthesia for spinal surgery. J Neurosurg Anesthesiol 2014;26:45–9.
[104] Gille O, Obeid I, Degrise C, Guerin P, Skalli W, Vital JM. The use of curare during anesthesia to prevent iatrogenic muscle damage caused by lumbar spinal surgery through a posterior approach. Spine 2007;32:402–5.
[105] Van Wijk RM, Watts RW, Ledowski T, Trochsler M, Moran JL, Arenas GW. Deep neuromuscular block reduces intra-abdominal pressure requirements during laparoscopic cholecystectomy: a prospective observational study. Acta Anaesthesiol Scand 2015;59:434–40.
[106] Bhananker SM, Treggiari MM, Sellers BA, Cain KC, Ramaiah R, Thilen SR. Comparison of train-of-four count by anesthesia providers versus TOF-Watch(R) SX: a prospective cohort study. Can J Anaesth 2015;62:1089–96.
[107] Larsen PB, Gätke MR, Fredensborg BB, Berg H, Engbaek J, Viby-Mogensen J. Acceleromyography of the orbicularis oculi muscle II: comparing the orbicularis oculi and adductor pollicis muscles. Acta Anaesthesiol Scand 2002;46:1131–6.
[108] Dhonneur G, Kirov K, Motamed C, Amathieu R, Kamoun W, Slavov V, et al. Post-tetanic count at adductor pollicis is a better indicator of early diaphragmatic recovery than train-of-four count at corrugator supercilii. Br J Anaesth 2007;99:376–9.
[109] Thilen SR, Hansen BE, Ramaiah R, Kent CD, Treggiari MM, Bhananker SM. Intraoperative neuromuscular monitoring site and residual paralysis. Anesthesiology 2012;117:964–72.
[110] Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. Anesth Analg 2005;100:1840–5.
[111] Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS, et al. Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. Anesth Analg 2013;117:133–41.
[112] Suzuki T, Fukano N, Kitajima O, Saeki S, Ogawa S. Normalization of acceleromyographic train-of-four ratio by baseline value for detecting residual neuromuscular block. Br J Anaesth 2006;96:44–7.
[113] Capron F, Fortier LP, Racine S, Donati F. Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. Anesth Analg 2006;102:1578–84.
[114] Arbous MS, Meursing AE, van Kleef JW, de Lange JJ, Spoormans HH, Touw P, et al. Impact of anesthesia management characteristics on severe morbidity and mortality. Anesthesiology 2005;102:257–68.
[115] Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg 2008;107:130–7.
[116] Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. BMJ 2012;345:e6329.
[117] Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. Anesthesiology 2016;125:647–55.
[118] Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, De Mel A, et al. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: sugammadex, neostigmine or no reversal. Eur J Anaesthesiol 2014;31:423–9.
[119] Eikermann M, Vogt FM, Herbstreit F, Vahid-Dastgerdi M, Zenge MO, Ochterbeck C, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. Am J Respir Crit Care Med 2007;175:9–15.
[120] Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anaesth 2010;105:304–9.
[121] Kirkeogaard H, Heier T, Caldwell J. Efficacy of tactile-guided reversal from cisatracurium induced neuromuscular block. Anesthesiology 2002;96:45–50.
[122] Kim KS, Cheong MA, Lee HJ, Lee JM. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane. Anesth Analg 2004;99:1080–5.
[123] Donati F, Smith CE, Bevan DR. Dose-response relationship for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 1989;68:13–9.
[124] Abdulatif M, Mowafi H, Al-Ghamdi A, El-Sanabary M. Dose-response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults. Br J Anaesth 1996;77:10–5.
[125] Harper NJN, Wallace M, Hall IA. Optimum dose of neostigmine at two levels of atracurium-induced neuromuscular block. Br J Anaesth 1994;72:82–5.
[126] Herbstreit F, Zigrahn D, Ochterbeck C, Petres J, Eikermann M. Neostigmine/glycopyrrolate administered after recovery from neuromuscular block increases upper airway collapsibility by decreasing genioglossus muscle activity in response to negative pharyngeal pressure. Anesthesiology 2010;113:1280–8.
[127] Fuchs-Buder T, Meistelman C, Alla F, Grandjean A, Wuthrich Y, Donati F. Antagonism of low degrees of atracurium-induced neuromuscular blockade: dose-effect relationship for neostigmine. Anesthesiology 2010;112:34–40.
[128] Choi ES, Oh AY, Seo KS, Hwang JW, Ryu JH, Koo BW, et al. Optimum dose of neostigmine to reverse shallow neuromuscular blockade with rocuronium and cisatracurium. Anaesthesia 2016;71:443–9.
[129] Caldwell JE. Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. Anesth Analg 1995;80:1168–74.
[130] Schaller SJ, Fink H, Ulm K, Blobner M. Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. Anesthesiology 2010;113:1054–60.
[131] Pongracz A, Szatmari S, Nemes R, Fulesdi B, Tassonyi E. Reversal of neuromuscular blockade with sugammadex at the reappearance of four twitches to train-of-four stimulation. Anesthesiology 2013;119:10–2.
[132] Sorgenfrei IF, Norrild K, Bo Larsen P, Stensballe J, Ostergaard D, Prins ME, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex. Anesthesiology 2006;104:667–74.
[133] Suy K, Morias K, Cammu G, Hans P, Duijnhoven WGF, Heeringa M, et al. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. Anesthesiology 2007;106:283–8.
[134] Groudine SB, Soto R, Lien C, Drover D, Roberts K. A randomized, dose-finding, phase II study of the selective relaxant binding drug, sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg 2007;104:555–62.
[135] Sparr HJ, Vermeyen KM, Beaufort AM, Rietbergen H, Proost JH, Saldien V, et al. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study. Anesthesiololy 2007;106:935–43.
[136] Puhringer FK, Rex C, Sielenkamper AW, Claudius C, Larsen PB, Prins M, et al. Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points. Anesthesiology 2008;109:188–97.
[137] de Boer HD, Driessen JJ, Marcus ME, Kerkkamp H, Heeringa M, Klimek M. Reversal of rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex. A multicenter, dose-finding and safety study. Anesthesiology 2007;107:239–44.
[138] Eleveld DJ, Kuizenga K, Proost JH, Wierda JMKH. A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. Anesth Analg 2007;104:582–4.
[139] Suzuki T, Kitajima O, Ueda K, Kondo Y, Kato J, Ogawa S. Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients. Br J Anaesth 2011;106:823–6.
[140] de Souza CM, Tardelli MA, Tedesco H, Garcia NN, Caparros MP, Alvarez-Gomez JA, et al. Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease. Eur J Anaesthesiol 2015;32:681–6.
[141] Mirzakhani H, Welch CA, Eikermann M, Nozari A. Neuromuscular blocking agents for electroconvulsive therapy: a systematic review. Acta Anaesthesiol Scand 2012;56:3–16.
[142] Mirzakhani H, Guchelaar HJ, Welch CA, Cusin C, Doran ME, MacDonald TO, et al. Minimum effective doses of succinylcholine and rocuronium during electroconvulsive therapy: a prospective, randomized, crossover trial. Anesth Analg 2016;123:587–96.
[143] Chow TKF. Titration of electroconvulsive therapy: the use of rocuronium and sugammadex with adjunctive laryngeal mask. Br J Anaesth 2012;108:882–3.
[144] Batistaki C, Kesidis K, Apostolaki S, Kostopanagiotou G. Rocuronium antagonized by sugammadex for series of electroconvulsive therapy (ECT) in a patient with pseudocholinesterase deficiency. J ECT 2011;27:e47–8.
[145] Lemmens H, Brodsky JB. The dose of succinylcholine in morbid obesity. Anesth Analg 2006;102:438–42.
[146] Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44:1051–65.
[147] Suzuki T, Masaki G, Ogawa S. Neostigmine-induced reversal of vecuronium in normal weight, overweight and obese female patients. Br J Anaesth 2006;97:160–3.
[148] Gaszynski T, Szewczyk T, Gaszynski W. Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. Br J Anaesth 2012;108:236–9.
[149] Van Lancker P, Dillemans B, Bogaert T, Mulier JP, De Kock M, Haspeslagh M. Ideal versus corrected body weight for dosage of sugammadex in morbidly obese patients. Anaesthesia 2011;66:721–5.
[150] Loupec T, Frasca D, Rousseau N, Faure JP, Mimoz O, Debaene B. Appropriate dosing of sugammadex to reverse deep rocuronium-induced blockade in morbidly obese patients. Anaesthesia 2016;71:265–72.
[151] Constant I, Louvet N, Guye ML, Sabourdin N. General anaesthesia in children: a French survey of practices. Ann Fr Anesth Reanim 2012;31:709–23.
[152] Aouad MT, Yazbeck-Karam VG, Mallat CE, Esso JJ, Siddik-Sayyid SM, Kaddoum RN. The effect of adjuvant drugs on the quality of tracheal intubation

without muscle relaxant in children: a systematic review of randomized trials. Paediatr Anaesth 2012;22:616–26.
[153] Julien-Marsollier F, Michelet D, Bellon M, Horlin AL, Devys JM, Dahmani S. Muscle relaxation for tracheal intubation during paediatric anaesthesia. Eur J Anesth 2017;34:1–12.
[154] Morgan JM, Barker I, Peacock JE, Eissa A. A comparison of intubating conditions in children following induction of anaesthesia with propofol and suxamethonium or propofol and remifentanil. Anaesthesia 2007;62:135–9.
[155] Blair JM, Hill DA, Wilson CM, Fee JP. Assessment of tracheal intubation in children after induction with propofol and different doses of remifentanil. Anaesthesia 2004;59:27–33.
[156] Crawford MW, Hayes J, Tan JM. Dose-response of remifentanil for tracheal intubation in infants. Anesth Analg 2005;100:1599–604.
[157] Steyn MP, Quinn AM, Gillespie JA, Miller DC, Best CJ, Morton NS. Tracheal intubation without neuromuscular block in children. Br J Anaesth 1994;72:403–6.
[158] Klemola UM, Hiller A. Tracheal intubation after induction of anesthesia in children with propofol – remifentanil or propofol-rocuronium. Can J Anaesth 2000;47:854–9.
[159] Annila P, Viitanen H, Reinikainen P, Baer G, Lindgren L. Induction characteristics of thiopentone/suxamethonium, propofol/alfentanil or halothane alone in children aged 13 years. Eur J Anaesthesiol 1999;16:359–66.
[160] Gelberg J, Kongstad L, Werner O. Intubation conditions in young infants after propofol and remifentanil induction with and without low-dose rocuronium. Acta Anaesthesiol Scand 2014;58:820–5.
[161] Batra YK, Al Qattan AR, Ali SS, Qureshi MI, Kuriakose D, Migahed A. Assessment of tracheal intubating conditions in children using remifentanil and propofol without muscle relaxant. Paediatr Anaesth 2004;14:452–6.
[162] Simon L, Boucebci KJ, Orliaguet G, Aubineau JV, Devys JM, Dubousset AM. Survey of practice of tracheal intubation without muscle relaxant in paediatric patients. Paediatr Anaesth 2002;12:36–42.
[163] Lerman J, Houle TT, Matthews BT, Houck J, Burrows FA. Propofol for tracheal intubation in children anesthetized with sevoflurane: a dose-response study. Paediatr Anaesth 2009;129:218–24.
[164] Gera S, Dali JS, Sharma KR, Garg R, Arya M. Evaluation of intubating conditions in children after sevoflurane induction using Propofol or rocuronium bromide: a randomised prospective, double blind study. Acta Anaesth Belg 2015;66:25–30.
[165] Politis GD, Stemland CJ, Balireddy RK, Brockhaus J, Hughes KR, Goins MD, et al. Propofol for pediatric tracheal intubation with deep anesthesia during sevoflurane induction: dosing according to elapsed time for two age groups. J Clin Anesth 2014;26:25–35.
[166] Politis GD, Frankland MJ, James RL, ReVille JF, Rieker MP, Petree BC. Factors associated with successful tracheal intubation in children with sevoflurane and non muscle relaxant. Anesth Analg 2002;95:615–20.
[167] Devys JM, Mourissoux G, Donnette FX, Plat R, Schauvliège F, Le Bigot P, et al. Intubating conditions and adverse events during sevoflurane induction in infants. Br J Anaesth 2011;106:225–9.
[168] Dewachter P, Mouton-Faivre C. Allergic risk during paediatric anaesthesia. Ann Fr Anesth Reanim 2010;29:215–26.
[169] Warner MA, Warner ME, Warner DO, Warner LO, Warner EJ. Perioperative pulmonary aspiration in infants and children. Anesthesiology 1999;90:66–71.
[170] Engelhardt T, Strachan L, Johnston G. Aspiration and regurgitation prophylaxis in paediatric anaesthesia. Paediatr Anaesth 2001;11:147–50.
[171] Hardman JG, Wills JS. The development of hypoxaemia during apnoea in children: a computational modelling investigation. Br J Anaesth 2006;97:564–70.
[172] Cheng CA, Aun CS, Gin T. Comparison of rocuronium and suxamethonium for rapid tracheal intubation in children. Paediatr Anaesth 2002;12:140–5.
[173] Klučka J, Štourač P, Štoudek R, Toukálková M, Harazim H, Kosinová M. Controversies in pediatric perioperative Airways. Biomed Res Int 2015;2015:368761.
[174] Gencorelli FJ, Fields RG, Litman RS. Complications during rapid sequence induction of general anesthesia in children: a benchmark study. Paediatr Anaesth 2010;20:421–4.
[175] Rawicz M, Brandom BW, Wolf A. Pro-con debate, the place of suxamethonium in pediatric anesthesia. Paediatr Anaesth 2009;19:561–70.
[176] Won YJ, Lim BG, Lee DK, Kim H, Kong MH, Lee IO. Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients: a systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e4678.
[177] Ammar AS, Mahmoud KM, Kasemy ZA. A comparison of sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children. Acta Anaesthesiol Scand 2017;61:374–80.
[178] Reitter M, Petitpain N, Latarche C, Cottin J, Massy N, Demoly P, et al. French network of regional pharmacovigilance centres. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy 2014;69:954–9.
[179] Dewachter P, Mouton-Faivre C. Anaphylaxis incidence with rocuronium, succinylcholine, and atracurium: how risk communication can influence behavior. Anesthesiology 2015;123:735–6.
[180] Mertes PM, Mouton-Faivre C. Anaphylaxis to neuromuscular-blocking drugs. All neuromuscular-blocking drugs are not the same. Anesthesiology 2015;122:5–7.
[181] Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. J Anesth 2016;30:290–7.
[182] Ledowski T, O'Dea B, Meyerkort L, Hegarty M, von Ungern-Sternberg BS. Postoperative residual neuromuscular paralysis at an Australian tertiary children's hospital. Anesthesiol Res Prac 2015;2015:410248.
[183] Gronert GA. Cardiac arrest after succinylcholine: mortality greater with rhabdomyolysis than receptor upregulation. Anesthesiology 2001;94:523–9.
[184] Blanié A, Ract C, Leblanc PE, Cheisson G, Huet O, Laplace C, et al. The limits of succinylcholine for critically ill patients. Anesth Analg 2012;115:873–9.
[185] Mégret F, Perrier V, Fleureau C, Germain A, Dewitte A, Rozé H, et al. Changes in kaliemia following rapid sequence induction with succinylcholine in critically ill patients. Ann Fr Anesth Reanim 2012;31:788–92.
[186] Baraka A, Tabboush Z. Neuromuscular response to succinylcholine-vecuronium sequence in three myasthenic patients undergoing thymectomy. Anesth Analg 1991;72:827–30.
[187] Eisenkraft JB, Book WJ, Mann SM, Papatestas AE, Hubbard M. Resistance to succinylcholine in myasthenia gravis: a dose-response study. Anesthesiology 1988;69:760–3.
[188] Smith CE, Donati F, Bevan DR. Cumulative dose-response curves for atracurium in patients with myasthenia gravis. Can J Anaesth 1989;36:402–6.
[189] Baraka A, Siddik S, Kawkabani N. Cisatracurium in a myasthenic patient undergoing thymectomy. Can J Anaesth 1999;46:779–82.
[190] Mann R, Blobner M, Jelen-Esselborn S, Busley R, Werner C. Preanesthetic train-of-four fade predicts the atracurium requirement of myasthenia gravis patients. Anesthesiology 2000;93:346–50.
[191] Wick S, Muenster T, Schmidt J, Forst J, Schmitt HJ. Onset and duration of rocuronium-induced neuromuscular blockade in patients with Duchenne muscular dystrophy. Anesthesiology 2005;102:915–9.
[192] Laycock JR, Smith CE, Donati F, Bevan DR. Sensitivity of the adductor pollicis and diaphragm muscles to atracurium in a hemiplegic patient. Anesthesiology 1987;67:851–3.
[193] de Boer HD, Shields MO, Booij LH. Reversal of neuromuscular blockade with sugammadex in patients with myasthenia gravis: a case series of 21 patients and review of the literature. Eur J Anaesthesiol 2014;31:715–21.
[194] de Boer HD, van Esmond J, Booij LH, Driessen JJ. Reversal of rocuronium-induced profound neuromuscular block by sugammadex in Duchenne muscular dystrophy. Paediatr Anaesth 2009;19:1226–8.
[195] Lepage JY, Malinge M, Cozian A, Pinaud M, Blanloeil Y, Souron R. Vecuronium and atracurium in patients with end-stage renal failure. A comparative study. Br J Anaesth 1987;59:1004–10.
[196] Proost JH, Eriksson LI, Mirakhur RK, Roest G, Wierda JM. Urinary, biliary and faecal excretion of rocuronium in humans. Br J Anaesth 2000;85:717–23.
[197] Staals LM, Snoeck MM, Driessen JJ, van Hamersvelt HW, Flockton EA, van den Heuvel MW, et al. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. Br J Anaesth 2010;104:31–9.
[198] Servin FS, Lavaut E, Kleef U, Desmonts JM. Repeated doses of rocuronium bromide administered to cirrhotic and control patients receiving isoflurane. A clinical and pharmacokinetic study. Anesthesiology 1996;84:1092–100.
[199] Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, et al. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology 1986;65:6–12.
[200] Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, et al. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 1984;61:699–702.
[201] Parker CJ, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 1989;62:177–83.
[202] Parker CJ, Jones JE, Hunter JM. Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. Br J Anaesth 1988;61:531–40.
[203] Kisor DF, Schmith VD, Wargin WA, Lien CA, Ornstein E, Cook DR. Importance of the organ-independent elimination of cisatracurium. Anesth Analg 1996;83:1065–71.
[204] Eastwood NB, Boyd AH, Parker CJ, Hunter JM. Pharmacokinetics of 1R-cis 1'R-cis atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. Br J Anaesth 1995;75:431–5.
[205] Kocabas S, Yedicocuklu D, Askar FZ. The neuromuscular effects of 0.6 mg kg^{-1} rocuronium in elderly and young adults with or without renal failure. Eur J Anaesthesiol 2008;25:940–6.
[206] Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure. Dose-response properties and interactions with azathioprine. Br J Anaesth 1987;59:995–1003.
[207] De Wolf AM, Freeman JA, Scott VL, Tullock W, Smith DA, Kisor DF, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 1996;76:624–8.
[208] Staals LM, Snoeck MM, Driessen JJ, Flockton EA, Heeringa M, Hunter JM. Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function. Br J Anaesth 2008;101:492–7.
[209] Cammu G, Van Vlem B, van den Heuvel M, Stet L, el Galta R, Eloot S, et al. Dialysability of sugammadex and its complex with rocuronium in intensive care patients with severe renal impairment. Br J Anaesth 2012;109:382–90.