The role of neuromuscular blockers in ARDS: benefits and risks

Sami Hraiech[a,b], *Jean-Marie Forel*[a,b], *and Laurent Papazian*[a,b]

Purpose of review
Neuromuscular blocking agents (NMBAs) are part of the pharmaceutical arsenal employed to treat acute respiratory distress syndrome (ARDS). However, their use remains controversial because the potential benefits of these agents are counterbalanced by possible adverse effects. This review summarizes advantages and risks of NMBAs based on the most recent literature.

Recent findings
NMBAs have been shown to improve oxygenation during severe ARDS in three randomized controlled trials. The most recent results demonstrated that NMBAs decrease 90-day in-hospital mortality, particularly in the most hypoxaemic patients. NMBAs have not been shown to be an independent risk factor of neuromyopathy in most studies.

Summary
NMBAs are commonly used in ARDS (25–55% of patients), but the benefits and the risks of using these agents are controversial. Recent data suggest that a continuous infusion of cisatracurium during the first 48 h of ARDS, particularly for patients with a P_aO_2/F_iO_2 ratio less than 120, can decrease 90-day in-hospital mortality. NMBAs do not appear to be an independent risk factor for ICU-acquired weakness if they are not given with corticosteroids or in patients with hyperglycaemia.

Keywords
acute respiratory distress syndrome, ICU-acquired weakness, mechanical ventilation, neuromuscular blocking agents

INTRODUCTION

Mortality in patients with acute respiratory distress syndrome (ARDS) remains high [1] despite significant advances, particularly in the management of mechanical ventilation [2,3]. One of the common nonventilatory strategies used in the treatment of ARDS is administration of neuromuscular blocking agents (NMBAs) [4]. There are no recent guidelines concerning the indication for use of NMBAs in ARDS [5], and use of these agents is controversial because of possible side effects, especially the development of ICU-acquired weakness [6]. However, interest in NMBAs has increased after a recent randomized controlled trial (RCT) [7] showed a reduction in 90-day adjusted mortality after a 48-h continuous infusion of cisatracurium besilate in the most severe ARDS patients. The debate on NMBAs has been revived, and the purpose of this review of the literature is to highlight the benefits and risks of NMBA use in ARDS.

BENEFITS OF NEUROMUSCULAR BLOCKING AGENTS IN ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS: WHAT IS THE EVIDENCE?

From reports of empirical use to randomized controlled studies, evidence is growing for the benefits of using paralysing agents to treat ARDS.

Adaptation to protective ventilation

Several reports highlight the frequent use of NMBAs for severe ARDS patients. In the Assessment of Low

[a]Aix-Marseille Univ, URMITE CNRS-UMR 6236 and [b]APHM, Hôpital Nord, Réanimation, Marseille, France

Correspondence to Laurent Papazian, Aix-Marseille Univ, URMITE CNRS-UMR 6236, 13005 Marseille, France; APHM, Hôpital Nord, Réanimation, 13015 Marseille, France. Tel: +33 4 91 96 58 35 or 36; fax: + 33 4 91 96 58 37; e-mail: laurent.papazian@ap-hm.fr

Curr Opin Crit Care 2012, 18:495–502

DOI:10.1097/MCC.0b013e328357efe1

KEY POINTS

- Administration of NMBAs in patients with early ARDS improves oxygenation and decreases 90-day in-hospital mortality, particularly in the most hypoxaemic patients (i.e. when P_aO_2/F_iO_2 ratio <120 mmHg).
- The mechanisms involved could include better adaptation to protective ventilation with less VILI and a diminution of inflammation.
- NMBAs do not appear to be an independent risk factor for ICU-acquired weakness if they are not given with corticosteroids or in patients with hyperglycaemia.

tidal Volume and increased End-expiratory volume to Obviate Lung Injury trial [8], NMBAs were used in 45 and 33% of patients in the lower and higher positive end-expiratory pressure (PEEP) groups, respectively [9]. A recent review reported that 25–55% of ARDS patients received adjuvant NMBAs [10]. One of the main reasons to justify the use of NMBAs in ARDS is facilitation of mechanical ventilation and control of patient/ventilator asynchrony [6,11▪]. Paralysing the patient to facilitate 'controlled ventilation' could prevent patient–ventilator dyssynchrony, improve adaptation to mechanical ventilation and enable tolerance of 'permissive' hypercapnia [12]. Indeed, even deep sedation is often not enough to control minute ventilation, plateau pressure and tidal volume in the first phase of ARDS. Arroliga *et al.* [9] showed that the factors associated with NMBA use were mainly related to the severity of the disease, as assessed by a high Acute Physiology, Age, Chronic Health Evaluation III score. Moreover, NMBAs are often used for prone positioning, high PEEP levels or nonconventional modes of ventilation, such as high-frequency oscillatory ventilation [13].

Improvement of oxygenation

Hypoxaemia is one of the most common reasons to use paralysing agents during ARDS [5]. In the early eighties, an improvement of oxygenation after administration of NMBAs was reported [14,15], but these results were not confirmed by subsequent studies [16]. A more recent study [17] reported an improvement in the P_aO_2/F_iO_2 ratio in ARDS patients 30 min and 2 h after introducing a continuous infusion of cisatracurium (GlaxoSmithKline, Uxbridge, UK). However, these studies lacked methodological reliability, either because of their design or the small number of patients included. In the past 10 years, the first RCT was published on the effect of NMBAs on oxygenation during ARDS, which served as the basis for strong support of their use in this setting.

There are, however, only three RCTs in the setting of lung-protective ventilation, and they were conducted by the same group of investigators (Table 1). The first trial was conducted by Gainnier *et al.* [18] on 56 patients with ARDS. In this multicentre RCT, patients treated with NMBAs for 48 h had a significant improvement in their P_aO_2/F_iO_2 ratio compared to the placebo group. Patients randomized to the NMBA group had a higher P_aO_2/F_iO_2 at 48, 96 and 120 h after randomization. In contrast, there was not a change in the P_aO_2/F_iO_2 ratio 1 h after randomization in the NMBA group. In a second multicentre, prospective, RCT designed to analyse the effects on inflammation of an early 48-h cisatracurium infusion in ARDS patients, the same group [19] confirmed a beneficial effect of NMBAs on oxygenation in 36 ARDS patients. A decrease in plateau pressure and PEEP and FiO_2 requirements during the 120-h study period were more marked in the NMBA group. Recently, the ARDS et curarisation systematique (ACURASYS) study [7] confirmed these results and amplified them, showing not only that the P_aO_2/F_iO_2 ratio on day 7 was higher in patients receiving a 48-h continuous cisatracurium infusion than in the control group, but this was also the first RCT to demonstrate that NMBAs reduced mortality associated with ARDS.

Reduction of mortality

In the first two RCTs [18,19], there was a strong tendency toward a reduction in the mortality rate for patients receiving cisatracurium compared with the placebo group. However, these two trials were designed to explore physiological and/or biological effects. The ACURASYS study was the very first trial designed to evaluate the effect of NMBAs on mortality. In this multicentre, double-blind trial [7], 339 patients presenting with severe ARDS within the previous 48 h (i.e. a P_aO_2/F_iO_2 ratio <150 mmHg with PEEP ≥ 5 cm H_2O) were randomly assigned to receive either cisatracurium besylate (177 patients) or placebo (162 patients) for 48 h. The group of patients treated early with cisatracurium for 48 h showed an improvement in the adjusted 90-day survival rate compared with those who received placebo. After adjusting for the baseline P_aO_2/F_iO_2 ratio, plateau pressure and the Simplified Acute Physiology Score II, the hazard ratio for death at 90 days in the cisatracurium group, compared with the placebo group, was 0.68 [95% confidence interval (CI) 0.48–0.98; $P = 0.04$]. Furthermore, the crude mortality rate at 28 days was 23.7% in patients who received cisatracurium and 33.3% in those who received placebo ($P = 0.05$) (Fig. 1 and Table 1). It

Table 1. Patient characteristics, study design, endpoints and main results of the three randomized controlled trials evaluating the efficacy of NMBAs on gas exchange, morbidity and mortality in patients with ARDS

Study (ref.), year	Population	Intervention	Main and secondary outcomes	Results
Gainnier *et al.* [18], 2004	$n=56$	Cisatracurium bolus 50 mg i.v., then 5 μg/kg/min infusion for 48 h ($n=28$) adapted for TOF = 0	Change in PaO_2/FiO_2 ratio	Improvement in PaO_2/FiO_2 ratio with cisatracurium ($P=0.021$)
	ARDS: P/F ≤ 150 with PEEP	Vs.	28 days mortality	35.7% with cisatracurium vs. 60.7% with placebo ($P=0.061$)
	≥5 cmH_2O	Placebo: 4 ml/h of normal saline ($n=28$)	ICU mortality	46.4% with cisatracurium vs. 71.4% with placebo ($P=0.057$)
	Age: 60.2 years		60 days mortality	46.4% with cisatracurium vs. 64.3% with placebo ($P=0.18$)
	MV: ARDSnet protocol		Days free of mechanical ventilation at 28 days	3.7 ± 7.2 with cisatracurium vs. 1.7 ± 5.3 days with placebo ($P=0.24$)
	Baseline Vt: 7.2 ml/kg PBW		Days free of mechanical ventilation at 60 days	19.0 ± 20.3 with cisatracurium vs. 9.8 ± 16.9 days with placebo ($P=0.071$)
	Baseline P/F ratio: 124		Barotrauma (n)	0 patient with cisatracurium vs.1 patient with placebo
	SAPS II: 44		ICU-acquired weakness (clinical, n)	0 patient with cisatracurium vs. 0 patient with placebo
	Sedation to Ramsay score of 6			
	Train of four (TOF) for monitoring of paralysis (0)			
Forel *et al.* [19] 2006	$n=36$	Cisatracurium bolus: 0.2 mg/kg, then 5 μg/kg/min for 48 h ($n=18$) adapted for TOF = 0	Pulmonary and systemic inflammatory response	Decrease in pulmonary (IL-1, 6, 8) and systemic (IL-1, 6) pro-inflammatory cytokines with cisatracurium
	ARDS: P/F ≤ 200 with PEEP	Vs.	Change in PaO_2/FiO_2 ratio	Improvement in PaO_2/FiO_2 ratio with cisatracurium ($P=0.019$)
	≥5 cmH_2O	Placebo infusion for 48 h ($n=18$)	28 days mortality	27.8% with cisatracurium vs. 55.6% with placebo ($P=$ NS)
	Age: 56.5 years		ICU mortality	27.8% with cisatracurium vs. 55.6% with placebo ($P=$ NS)
	MV: ARDSnet protocol		Duration of mechanical ventilation	20.0 ± 11.6 with cisatracurium vs. 18.0 ± 8.3 days with placebo ($P=$ NS)
	Baseline Vt: 6.8 ml/kg PBW		Days free of mechanical ventilation at 28 days	6.0 ± 8.6 with cisatracurium vs. 5.4 ± 6.4 days with placebo ($P=$ NS)
	SAPS II: 48		Barotrauma (n)	0 patient with cisatracurium vs. 0 patient with placebo
	Sedation to Ramsay score of 6		ICU-acquired weakness (clinical, n)	1 patient with cisatracurium vs. 1 patient with placebo
	TOF for monitoring of paralysis (0)			
Papazian *et al.* [7] 2010	$n=339$	Cisatracurium bolus 15 mg i.v., then 37.5 mg/h (7.5 ml/h) infusion for 48 h ($n=177$)	Adjusted 90-day mortality	HR 0.68; 95% CI (0.48–0.98) ($P=0.04$) adjusted for baseline PaO_2/FiO_2, plateau airway pressure, and Simplified Acute Physiology Score II
	ARDS: P/F ≤ 150 with PEEP	Vs.	28-day mortality	23.7% with cisatracurium vs. 33.3% with placebo ($P=0.05$)

Table 1 (*Continued*)

Study (ref.), year	Population	Intervention	Main and secondary outcomes	Results
	≥ 5 cmH_2O	Placebo ($n=162$): 7.5 ml/h of normal saline	ICU mortality	29.4% with cisatracurium vs. 38.9% with placebo ($P=0.06$)
	Age: 58 years		Days free of mechanical ventilation at 28 days	10.6 ± 9.7 with cisatracurium vs. 8.5 ± 9.4 days with placebo ($P=0.04$)
	MV: ARDSnet protocol		Days free of mechanical ventilation at 90 days	53.1 ± 35.8 with cisatracurium vs. 44.6 ± 37.5 days with placebo ($P=0.03$)
	Baseline Vt: 6.5 ml/kg PBW		Change in PaO_2/FIO_2 ratio	Improvement in PaO_2/FIO_2 ratio with cisatracurium ($P<0.05$)
	Baseline P/F ratio: 110		Barotrauma [%(IQR)]	5.1% (2.7–9.4) with cisatracurium vs. 11.7% (7.6–17.6) with placebo ($P=0.03$)
	SAPS II: 48.5		Patients without ICU-acquired weakness by ICU discharge [% (IQR)]	64.3% (55.1–72.6) with cisatracurium vs. 68.5% (58.3–77.3) with placebo ($P=0.51$)
	Sedation to Ramsay score of 6			
	No TOF for monitoring of paralysis			
	Weaning from MV: protocol			
	ICU-acquired weakness evaluated by MRC score			

ARDS, acute respiratory distress syndrome; HR, hazard ratio; MRC score, Medical Research Council score; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; P/F, PaO_2/FiO_2 ratio; PBW, predicted body weight; TOF, train of four; Vt, tidal volume.

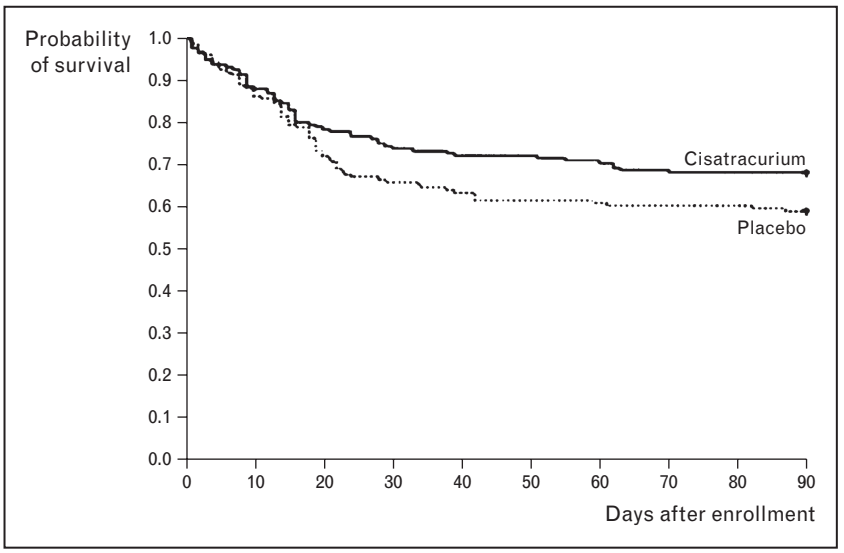

FIGURE 1. Probability of survival through day 90 in 339 early ARDS patients randomized to receive a 48-h cisatracurium infusion or placebo. The Cox regression model after adjustment for the baseline P_aO_2/F_iO_2 ratio, SAPS II and plateau pressure yielded a hazard ratio for death at 90 days in the cisatracurium group of 0.68 [95% confidence interval (CI) 0.48–0.98; $P=0.04$] compared with the placebo group. ARDS, acute respiratory distress syndrome. Reproduced from [7] with permission.

is noteworthy that the beneficial effect of cisatracurium on mortality was limited to the patients presenting a P_aO_2/F_iO_2 ratio of less than 120. Among these patients, the 90-day mortality was 30.8% in the cisatracurium group and 44.6% in the control group ($P = 0.04$) [7].

With respect to the secondary endpoints, patients in the cisatracurium group had significantly more ventilator-free days than those in the placebo group during the first 28 and 90 days and more days free of organ failure (other than the lung) during the first 28 days. Patients in the cisatracurium group had also fewer pneumothoraces than those in the placebo group (11.7 vs. 4.0% in the cisatracurium group; $P = 0.01$).

Possible mechanisms of action explaining the beneficial effects

The observed improvements in mortality and gas exchange raise the question of the mechanisms involved. There are several potential pathophysiological pathways involved, and they are likely interrelated. Slutsky [12] proposed that paralysing agents could limit ventilator-induced lung injury (VILI), decrease blood flow to active muscle groups and improve arterial oxygenation, have a direct or indirect anti-inflammatory effect and decrease the occurrence of multiorgan failure by limiting biotrauma.

NMBAs modify thoraco-pulmonary mechanics and could improve the ventilation-to-perfusion ratio. The increase in thoraco-pulmonary compliance in ARDS can increase the functional residual capacity (FRC) and decrease the intrapulmonary shunt [20].

The positive effects of NMBAs could also be related to a decrease in VILI (i.e. atelectrauma, barotrauma, volutrauma and biotrauma) [21], as shown by the decreased incidence of barotrauma and pneumothoraces in the cisatracurium group in the ACURASYS study. It is now accepted that lung-protective mechanical ventilation decreases inflammation and mortality in patients with ARDS [22]. NMBA use could reinforce this beneficial effect of lung-protective mechanical ventilation in patients with ARDS through a reduction in biotrauma. This hypothesis was supported by Forel *et al.* [19]. In this study, 48 h after randomization, pulmonary concentrations of IL-1β, IL-6 and IL-8, as well as serum concentrations of IL-1β and IL-6 were lower in the NMBA group than in the control group. This finding is reinforced by the decrease in number of organ failures for patients in the cisatracurium group of the ACURASYS study, possibly as a result of less biotrauma [7]. Nevertheless, the direct anti-inflammatory effects of NMBAs remain unclear.

NMBAs could help to avoid patient–ventilator dyssynchrony and limit end-expiratory collapse by inhibiting active expiration, limiting derecruitment and maintaining PEEP [12]. Moreover, in some patients, inspiratory efforts could lead to global or regional increases in transpulmonary pressure (TPP) that can be deleterious [23▪]. In lavage-injured rabbits, Yoshida *et al.* [23▪] showed that spontaneous breathing efforts associated with moderate tidal volumes (7–9 ml/kg) generating high TPP were associated with significant lung injuries, even when the plateau pressure was maintained below 30 cmH_2O.

These recent data from the literature provide a strong argument for beneficial effects of NMBAs during the early phase of severe ARDS, and support the use of a 48-h infusion of cisatracurium in patients with more hypoxaemic ARDS (particularly with a P_aO_2/F_iO_2 ratio <120 mmHg). However, risks of using NMBAs have been reported and have resulted in controversy regarding the use of these agents for patients with ARDS. These risks warrant further attention.

RISKS ASSOCIATED WITH NEUROMUSCULAR BLOCKING AGENT USE: ARE THE BENEFITS WORTH THE RISKS?

Side effects of NMBAs in ICU patients have been a topic of discussion over the past 10 years. Figure 2 illustrates the main benefits and risks described in the literature.

ICU-acquired weakness

In a recent review evaluating the importance of polyneuropathy and myopathy in critical care, the incidence of ICU-acquired weakness was 34–60% in patients with ARDS [24▪▪]. ICU-acquired weakness is responsible for severe and durable morbidity, such as limb and diaphragm weakness, that can persist for months or even years after discharge from the ICU [25]. As a result, since it was first described in the early eighties, ICU neuromyopathy has become a major concern [26]. Risk factors have been discussed in the literature. Some independent risk factors include female sex, multiple organ dysfunctions (≥ 2), duration of mechanical ventilation and administration of corticosteroids [27]. It would appear that immobilization (favoured by NMBAs) renders the muscles more sensitive to the action of corticoids [28]. Glucocorticoids have catabolic effects on skeletal muscles and induce muscle atrophy [29]. Moreover, Kindler *et al.* [30] showed an additive effect of methylprednisolone or hydrocortisone and vecuronium on the acetylcholine

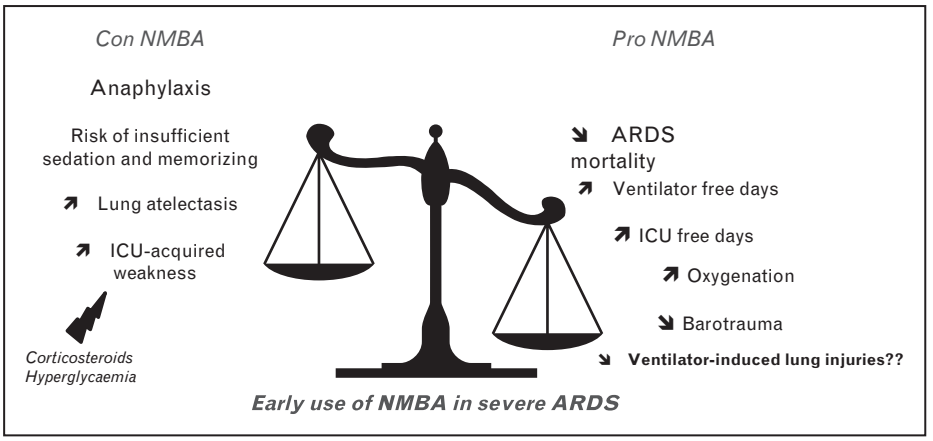

FIGURE 2. Benefits and risks balance of the use of NMBAs in ARDS patients. ARDS, acute respiratory distress syndrome; NMBAs, neuromuscular blocking agents.

receptor. Duration of vasopressor support, duration of ICU stay, hyperglycaemia, low serum albumin and neurological failure have also been identified as risk factors [31–33]. Bercker *et al.* [34] demonstrated that blood glucose levels during 28 days of an ICU stay were significantly higher in patients who developed neuromyopathy than in control patients. With respect to NMBAs, the literature is contradictory. Axonal neuropathies have rarely been associated with only NMBA administration. In a population of 95 patients, De Jonghe *et al.* [35] found that NMBAs were not associated with muscular weakness. In a recent prospective observational study performed in 40 ICUs, Weber-Carstens *et al.* [36] showed that NMBA use was not a significant risk factor for the development of impaired muscle membrane excitability. It is noteworthy that the association between NMBAs and corticosteroids seems to favour neuromuscular lesions. Griffiths and Hall [37] reported that simultaneous use of NMBAs and corticosteroids could be associated with muscle weakness, whereas NMBA use alone was not identified as an independent risk factor. In the ACURASYS study [7], the incidence of ICU-acquired paresis (evaluated based on the Medical Research Council [27] score on day 28 or at the time of ICU discharge) was not higher in patients receiving a 48-h continuous cisatracurium infusion than in the control group. However, in one study, the use of NMBAs was an independent factor for ICU-acquired myopathies, but this study was performed on septic patients with multiple organ dysfunction, which is itself a risk factor for ICU weakness [38]. Hermans *et al.* [39] also identified NMBAs as an independent risk factor. Steroid compounds [vecuronium, pancuronium, rocuronium (Organon Pharmaceuticals, Roseland, NJ, USA)] appear to further favour the occurrence of myopathies because of their structural analogy [40]. A length of infusion exceeding 48 h is also a risk factor [41].

Increase in the duration of mechanical ventilation

In a retrospective study by Arroliga *et al.* [9], authors reported that unlike the use of sedatives and opioids, the use of NMBAs was not associated with prolonged exposure to mechanical ventilation. Furthermore, in the ACURASYS [7] study, the cisatracurium group had significantly more ventilator-free days than the placebo group during the first 28 and 90 days.

Diaphragm paralysis and lung atelectasis

The effects of NMBAs on thoraco-pulmonary morphology have been investigated. Several studies indicate that the use of NMBAs associated with sedation could be responsible for the occurrence of lung atelectasis. This has been investigated particularly in patients with healthy lungs in whom atelectasis occurs rapidly after anaesthesia with muscular paralysis [21]. Tokics *et al.* [20] described the presence of a shunt located to the gravity-dependent atelectatic lung regions during anaesthesia with muscle paralysis. Lung atelectasis linked to the loss of diaphragmatic tone was observed by Brismar *et al.* [42]. However, these morphologic abnormalities totally disappeared after the application of PEEP (10 cmH_2O) for 5 min [43]. The improvement in oxygenation observed in RCTs does not support a deleterious effect of NMBA on lung aeration. Imaging studies in patients with severe ARDS are necessary to draw conclusions about the effects of NMBAs on aeration of the lung.

Anaphylaxis risk

Hypersensitivity reactions occurring after administration of NMBAs are a major cause for concern. According to the US Food and Drug Administration (Reference ID 2867714), the main hypersensitivity symptoms that develop after administration of cisatracurium besilate are the following: hypotension 0.2%, flushing 0.2%, respiratory bronchospasm 0.2% and dermatological rash 0.1%. A recent survey [44] of hypersensitivity reactions observed during anaesthesia in 1253 French patients, all of whom experienced anaphylaxis, revealed that succinylcholine ($n = 226$; 60.6%) was the NMBA that most commonly caused anaphylaxis, whereas cisatracurium caused this reaction very infrequently ($n = 22$; 5.9%).

Insufficient sedation and memorizing

Paralysing patients highlights the problem of inadequate sedation. Hardin *et al.* [45] have demonstrated that patients receiving NMBAs were awake for 22% of the sleep period over a time span of 24 h. Neuromonitoring with continuous electro-encephalogram or a device, such as the Bispectral Index (BIS, Aspect Medical Systems, Natick, MA, USA), could reduce the risk of consciousness in paralysed patients [46]. A recent prospective controlled study [47] showed that a neuromuscular blocker did not alter the BIS score in deeply sedated patients, suggesting that this may be a reliable tool to monitor the level of sedation in paralysed patients.

Post-traumatic distress syndrome

Nelson *et al.* [48] investigated the relation between the use of NMBAs during acute lung injury (ALI) and the quality of life of survivors in a retrospective study of 24 patients, questioned 6–41 months after treatment in the ICU. Interestingly, post-traumatic stress disorder symptoms were positively correlated with days of sedation and days of NMBA use, but not with initial severity of illness. A possible explanation is that patients who were on NMBAs for longer periods were the same patients with the most complicated ICU course, which would increase the likelihood of exposure to distressing experiences.

CONCLUSION

Recent studies indicate that the use of NMBAs during the early phase of ARDS, especially in the most hypoxaemic patients (patients with a P_aO_2/F_iO_2 ratio <120 mmHg), improves oxygenation and decreases the 90-day mortality rate. The risks associated with the use of NMBAs can be limited by shortening the duration of administration to the first 48 h of ARDS. Administration of NMBAs does not appear to be an independent risk factor for ICU-acquired weakness if they are not given with corticosteroids or in patients with hyperglycaemia. The mechanisms underlying the beneficial effects of NMBAs remain unclear, and future studies will be necessary to investigate them further. However, the administration of NMBAs for 48 h in patients with early and severe ARDS appears to be beneficial and well tolerated and may be included in future recommendations.

Acknowledgements

None.

Conflicts of interest

Financial disclosure: Laurent Papazian received 30k€ from GlaxoSmithKline for the ACURASYS study. GlaxoSmithKline also provided the cisatracurium and placebo for the ACURASYS study.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 573).

1. Phua J, Badia JR, Adhikari NK, *et al.* Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. Am J Respir Crit Care Med 2009; 179:220–227.
2. Esan A, Hess DR, Raoof S, *et al.* Severe hypoxemic respiratory failure: part 1: ventilatory strategies. Chest 2010; 137:1203–1216.
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–1308.
4. Arroliga A, Frutos-Vivar F, Hall J, *et al.* Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest 2005; 128:496–506.
5. Murray MJ, Cowen J, DeBlock H, *et al.* Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002; 30:142–156.
6. Vender JS, Szokol JW, Murphy GS, *et al.* Sedation, analgesia, and neuromuscular blockade in sepsis: an evidence-based review. Crit Care Med 2004; 32:S554–S561.
7. Papazian L, Forel JM, Gacouin A, *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–1116.
8. Brower RG, Lanken PN, MacIntyre N, *et al.* Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–336.
9. Arroliga AC, Thompson BT, Ancukiewicz M, *et al.* Use of sedatives, opioids, and neuromuscular blocking agents in patients with acute lung injury and acute respiratory distress syndrome. Crit Care Med 2008; 36:1083–1088.
10. Raoof S, Goulet K, Esan A, *et al.* Severe hypoxemic respiratory failure: part 2: nonventilatory strategies. Chest 2010; 137:1437–1448.
11. ■ Needham CJ, Brindley PG. Best evidence in critical care medicine: the role of neuromuscular blocking drugs in early severe acute respiratory distress syndrome. Can J Anaesth 2012; 59:105–108.

This recent article offers an analysis of the ACURASYS study based on methodology and relevance to clinical practice. It also includes a brief current state of the literature in the field.

12. Slutsky AS. Neuromuscular blocking agents in ARDS. N Engl J Med 2010; 363:1176–1180.
13. Mehta S, Granton J, MacDonald RJ, *et al.* High-frequency oscillatory ventilation in adults: the Toronto experience. Chest 2004; 126:518–527.

14. Pollitzer MJ, Reynolds EO, Shaw DG, Thomas RM. Pancuronium during mechanical ventilation speeds recovery of lungs of infants with hyaline membrane disease. Lancet 1981; 1:346–348.
15. Coggeshall JW, Marini JJ, Newman JH. Improved oxygenation after muscle relaxation in adult respiratory distress syndrome. Arch Intern Med 1985; 145:1718–1720.
16. Philips JB, Setzer ES, Drummond WH, *et al.* Hypoxaemia in ventilated neonates after pancuronium paralysis. Lancet 1979; 1:877.
17. Lagneau F, D'honneur G, Plaud B, *et al.* A comparison of two depths of prolonged neuromuscular blockade induced by cisatracurium in mechanically ventilated critically ill patients. Intensive Care Med 2002; 28:1735–1741.
18. Gainnier M, Roch A, Forel JM, *et al.* Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004; 32:113–119.
19. Forel JM, Roch A, Marin V, *et al.* Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006; 34:2749–2757.
20. Tokics L, Hedenstierna G, Svensson L, *et al.* V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 1996; 81:1822–1833.
21. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006; 32:24–33.
22. Parsons PE, Eisner MD, Thompson BT, *et al.* Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005; 33:1–6.
23. ▪ Yoshida T, Uchiyama A, Matsuura N, *et al.* Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit Care Med 2012; 40:1578–1585.

In this experimental work, authors show the potential deleterious effects of uncontrolled spontaneous breathing efforts during protective ventilation of ALI.

24. ▪▪ Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol 2011; 10:931–941.

In this recent review, authors develop the epidemiology, risk factors and outcomes of ICU-acquired weakness.

25. Latronico N, Shehu I, Seghelini E. Neuromuscular sequelae of critical illness. Curr Opin Crit Care 2005; 11:381–390.
26. Bolton CF. The discovery of critical illness polyneuropathy: a memoir. Can J Neurol Sci 2010; 37:431–438.
27. De Jonghe B, Sharshar T, Lefaucheur JP, *et al.* Paresis acquired in the intensive care unit: a prospective multicenter study. J Am Med Assoc 2002; 288:2859–2867.
28. Latronico N, Guarneri B. Critical illness myopathy and neuropathy. Minerva Anesthesiol 2008; 74:319–323.
29. Jackman RW, Kandarian SC. The molecular basis of skeletal muscle atrophy. Am J Physiol Cell Physiol 2004; 287:834–843.
30. Kindler CH, Verotta D, Gray AT, *et al.* Additive inhibition of nicotinic acetylcholine receptors by corticosteroids and the neuromuscular blocking drug vecuronium. Anesthesiology 2000; 92:821–832.
31. Witt NJ, Zochodne DW, Bolton CF, *et al.* Peripheral nerve function in sepsis and multiple organ failure. Chest 1991; 99:176–184.
32. Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. Curr Opin Crit Care 2005; 11:126–132.
33. Van den Berghe G, Schoonheydt K, Becx P, *et al.* Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005; 64:1348–1353.
34. Bercker S, Weber-Carstens S, Deja M, *et al.* Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med 2005; 33:711–715.
35. De Jonghe B, Lacherade JC, Sharshar T, *et al.* Intensive care unit-acquired weakness: risk factors and prevention. Crit Care Med 2009; 37:S309–315.
36. Weber-Carstens S, Deja M, Koch S, *et al.* Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit Care 2010; 14:R119.
37. Griffiths RD, Hall JB. Intensive care unit-acquired weakness. Crit Care Med 2010; 38:779–787.
38. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, *et al.* Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med 2005; 33:349–354.
39. Hermans G, Wilmer A, Meersseman W, *et al.* Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med 2007; 175:480–489.
40. Testelmans D, Maes K, Wouters P, *et al.* Infusions of rocuronium and cisatracurium exert different effects on rat diaphragm function. Intensive Care Med 2007; 33:872–879.
41. Hansen-Flaschen J. Neuromuscular blockade in the intensive care unit. More than we bargained for. Am Rev Respir Dis 1993; 147:234–236.
42. Brismar B, Hedenstierna G, Lundquist H, *et al.* Pulmonary densities during anesthesia with muscular relaxation–a proposal of atelectasis. Anesthesiology 1985; 62:422–428.
43. Hedenstierna G, Strandberg A, Brismar B, *et al.* Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. Anesthesiology 1985; 62:247–254.
44. Dong SW, Mertes PM, Petitpain N, *et al.* Hypersensitivity reactions during anaesthesia. Results from the ninth French survey (2005–2007). Minerva Anestesiol 2012 [Epub ahead of print].
45. Hardin KA, Seyal M, Stewart T, *et al.* Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. Chest 2006; 129:1468–1477.
46. Ballard N, Robley L, Barrett D, *et al.* Patients' recollections of therapeutic paralysis in the intensive care unit. Am J Crit Care 2006; 15:86–94.
47. Inoue S, Kawaguchi M, Sasaoka N, *et al.* Effects of neuromuscular block on systemic and cerebral hemodynamics and bispectral index during moderate or deep sedation in critically ill patients. Intensive Care Med 2006; 32:391–397.
48. Nelson BJ, Weinert CR, Bury CL, *et al.* Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med 2000; 28:3626–3630.