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A comparison of two depths of prolonged neuromuscular blockade induced by cisatracurium in mechanically ventilated critically ill patients

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Abstract *Objectives:* To compare two levels of continuous cisatracurium-induced curarization in hypoxemic, ventilated patients. *Design and setting:* An open-labeled, multicenter, prospective, randomized study. *Patients:* Hundred two patients with a ratio between arterial oxygen tension and inspired oxygen tension (PaO_2/FIO_2) less than 200 despite optimization of sedation and ventilation were randomized into group 1 (n=52) with an end point of no response at orbicularis oculi to train-of-four (TOF) stimulation or group 2 (n=50) with an end point of two responses. *Measurements and results:* The PaO_2/FIO_2 and end-inspiratory plateau airway pressure (Pplat) were evaluated at baseline (before curarization) and at regular intervals once TOF end points had been attained for up to 2 h afterwards (T2 h). A decrease of 1 cmH_2O or more of Pplat at T2 h compared to baseline was observed in 37% and 50% of the patients in groups 1 and 2, respectively (p=0.17). Time courses of PaO_2/FIO_2 (mmHg) and Pplat (cmH_2O) [mean (SD)] were equivalent in both groups, with a mild increase in PaO_2/FIO_2 [p=0.0014; from 126 (33) to 141 (55) and from 134 (40) to 152 (52), respectively, in groups 1 and 2] and decrease in Pplat [p=0.016; from 29.1 (8.9) to 28.5 (8.8) and from 27.7 (7.5) to 26.6 (7.6)]. Median total durations of curarization were 28.9 h (3.1–219.7) in group 1 and 31.4 h (1.6–650.6) in group 2. Median cisatracurium infusion rates were 5.2 μg kg^{-1} min^{-1} (2.1–13.7) in group 1 and 3.6 μg kg^{1} min^{-1} (1.0–13.5) in group 2. The median delay to recovery from paralysis was shorter in group 2 (0.75 h vs 1.25 h; p=0.0008). *Conclusion:* When a prolonged curarization is decided upon in an ICU patient, a blockade at 2/4 at TOF at orbicularis oculi has similar effects on respiratory parameters as a blockade at 0/4, allowing a decrease in total administered doses and a shortening of the recovery of muscle strength after cessation of infusion.

Keywords Intensive care unit (ICU) · Mechanical ventilation · Neuromuscular blockade · Cisatracurium · Train-of-four (TOF) · Depth of blockade

Introduction

Although data clearly proving the beneficial effects of continuous neuromuscular blockade are still lacking in critically ill patients [1, 2, 3], 5–10% of mechanically ventilated patients are curarized in intensive care units (ICUs) [4, 5]. Further studies investigating such effects are, thus, of great importance. However, a pragmatic parallel approach could be to optimize the administration of neuromuscular blocking agents in ICU patients when a curarization is decided upon by the intensivist. Specifically, the optimal depth of neuromuscular blockade has not been determined. If an intermediate depth of neuromuscular blockade could provide equivalent effects upon respiratory parameters as a deep one, it could be clinically interesting as an overdose would be avoided, decreasing total infused doses of neuromuscular blocking agents and decreasing delays for recovery from muscle paralysis. This study was therefore designed to compare the effects of two depths of continuous neuromuscular blockade with cisatracurium on the PaO_2/FIO_2 ratio and end-inspiratory plateau airway pressure (Pplat) in mechanically ventilated patients often considered by the intensivists as requiring a prolonged muscle paralysis.

Materials and methods

Following the approval of local and national ethics committees and written informed consent from family members or surrogates, mechanically ventilated patients aged over 18 years with PaO_2/FIO_2 ratios less than 200, despite optimization of sedation (Ramsay score between 4 and 6) [6] and mechanical ventilation, were prospectively included. Specifically, the patient's breathing had to be synchronous with the ventilator before inclusion. Patients were excluded from the study if they had received a neuromuscular blocking agent within the previous 12 h, if they had received or were receiving high frequency ventilation or pressure control ventilation treatment or if they had an expected survival of less than 2 days. Other exclusion criteria included pregnancy, severe asthmatic attack, neuromuscular disorders, suspected allergy to cisatracurium, atracurium or benzene sulfonic acid and participation in another clinical trial within the previous 30 days.

Neuromuscular function was monitored by visual estimation of the contractions of orbicularis oculi in response to a calibrated facial train-of-four (TOF) stimulation. A 40 mA current intensity was delivered using a peripheral nerve stimulator (Innervator NS252F, Fisher-Paykel Health Care, Baxter, Maurepas, France). If visible contractions of the orbicularis oculi were not present at this current intensity before the start of neuromuscular blockade, a higher intensity (60–80 mA) was applied. Cutaneous electrodes (RedNot, 3 M Health Care, Borken, Germany), used to stimulate the facial nerve, were carefully positioned after the skin had been soaped and dried. Electrodes were systematically replaced every 6 h to ensure that good electrical conductivity was maintained.

Patients were assigned to study treatment in accordance with a randomization schedule. Treatment groups were assigned to blocks of four patients at each study center through a central facility. The treatment group for a given patient was determined by the investigator at that center opening a sealed envelope containing details of the allocated treatment. Patients were allocated to one of two treatment groups: group 1, with an end point for neuromuscular blockade of 0/4 response to TOF stimulation, and group 2 with an end point of 2/4 responses to TOF stimulation. In both groups, an initial bolus dose of cisatracurium besylate (Nimbex, GlaxoSmithKline, France) 0.1 mg kg^{-1} was administered followed by additional boluses of 0.05 mg kg^{-1} until the TOF response was at 3/4 or less. A continuous infusion of cisatracurium was then started at 3 μg kg^{-1} min^{-1}. The cisatracurium infusion rate was then adjusted as required to attain and maintain 0/4 response to TOF stimulation in group 1 and 2/4 responses in group 2. In order to avoid administering an excessive dose of cisatracurium to patients in group 1, a post-tetanic count (PTC) stimulation was also performed in this group, the required end point being one to two responses to PTC.

An initial period of 30 min allowed titration of the cisatracurium infusion rate to reach the required level of neuromuscular blockade. Thereafter, during a 2h period (the evaluation period), the infusion rate was titrated for each patient according to TOF responses recorded every 15 min in order to maintain the allocated depth of neuromuscular blockade. During this period, the patient's ventilator settings (respiratory rate, tidal volume, positive end-expiratory pressure and FIO_2) remained unchanged. After this period, the depth of neuromuscular blockade was monitored by TOF at orbicularis oculi at least twice daily, with titration of the infusion rate as needed to maintain the allocated depth of blockade. When the intensivist considered that neuromuscular blockade was no longer indicated clinically, the TOF response at orbicularis oculi was measured just before discontinuation of cisatracurium infusion and TOF monitoring was further applied at the adductor pollicis instead of the orbicularis oculi, in order to monitor the recovery from muscle paralysis. TOF monitoring at adductor pollicis was performed every 15 min until four responses had been obtained. A double-burst stimulation was then delivered every 15 min until two equivalent responses had been obtained. This was considered to indicate near complete recovery from neuromuscular blockade [7].

Concomitant sedation associated midazolam 5–20 mg h^{-1} and fentanyl 100–300 μg h^{-1} (or sufentanil 10–30 μg h^{-1}). Doses were unchanged from the start of cisatracurium infusion until the end of the evaluation period, after which they were adjusted according to the patient's needs.

Measurements

The following parameters were recorded before cisatracurium infusion: patient's demographic data (sex, age, weight), the origin of acute respiratory failure and his/her highest simplified acute physiologic score (SAPS II) during the previous 24 h before study entry.

Respiratory effects were assessed by measurements of PaO_2/FIO_2 and Pplat (cmH_2O) during a zero flow inspiratory hold. All recorded values of Pplat were the mean of three consecutive values read from the ventilator manometer by a physician who was unaware of the patient's allocated treatment group. The precision for Pplat readings was of 1 cmH_2O. PaO_2/FIO_2 and Pplat were recorded before cisatracurium infusion, immediately before the start of the evaluation period, immediately after the start of the evaluation period (T0) and every 15 min during the evaluation period. Heart rate, systolic, diastolic and mean arterial pressures (mmHg) were recorded before cisatracurium infusion, immediately before and after the start of the evaluation period, then every 15 min during this period. The time to recovery from neuromuscular blockade (time between cessation of the cisatracurium period and obtaining two equivalent responses at a double-burst stimulation at adductor pollicis) was recorded for each patient and was related to the duration of infusion.

Study end points

The primary end point was the percentage of patients presenting with a decrease in Pplat of 1 cmH_2O or more from the beginning to

Table 1 Patient demographic and clinical characteristics of intent-to-treat population (*SD* standard deviation, *APS II* Simplified Acute Physiologic Score II)

	Group 1 (*n*=52)	Group 2 (*n*=50)
Gender		
Male	42 (81%)	37 (74%)
Female	10 (19%)	13 (26%)
Age (years; mean (SD))	56 (17)	56 (16)
Weight (kg; mean (SD))	80 (16)	77 (17)
SAPS II score		
At time of admission to ICU (median (range))	41 (6–95)	40 (10–73)
At time of inclusion in study (median (range))	46 (14–76)	43 (18–76)
Origin of the acute respiratory failure		
Medical	18 (35%)	27 (54%)
Surgical	24 (46%)	17 (34%)
Polytrauma	10 (19%)	6 (12%)
Midazolam infusion rate (mg h^{-1}; mean (SD))	8.7 (5.1)	9.3 (8.0)
Fentanyl infusion rate (μg h^{-1}; mean (SD))	194 (78)	206 (101)
Sufentanil infusion rate (μg h^{-1}; mean (SD))	30 (12)	31 (23)

the end of the evaluation period. Secondary end points were time courses of PaO_2/FIO_2, Pplat and hemodynamic parameters during the same period. The results of TOF monitoring compared with the required end points in each group and the number of cisatracurium infusion rate modifications required to maintain these end points were also analyzed, as well as the time to recovery from neuromuscular blockade after discontinuation of the cisatracurium infusion, the incidence of adverse events during cisatracurium infusion (as reported by the investigators) and mortality from the start of cisatracurium infusion until the time the patient left the ICU.

Statistical analyses

For an expected decrease in Pplat in 60% of the patients in group 1 and 40% of the patients in group 2, and alpha and beta risks of 5% and 20%, respectively, the required number of patients in each group was fixed at 97. The safety population included all patients who received at least one bolus dose of cisatracurium. The intent-to-treat population comprised the patients who received cisatracurium and had Pplat recorded during the evaluation period. Categorical variables were summarized by frequencies. Continuous variables were summarized by means ± standard deviation (SD) if normally distributed or median (ranges) when normality could not be assumed. Percentages of patients with a decrease in Pplat during the evaluation period were compared between groups using a chi-square test. Change in Pplat during the evaluation period was tested by analysis of variance for repeated values, time effect and group effect being tested. If a time effect was significant, specific contrasts were tested between T2 h and before cisatracurium infusion, T0 and before infusion, and T2 h and T0 in both groups. The same method was used to test the time course of values for PaO_2/FIO_2. The incidences of adverse effects and of mortality were presented. Statistical analysis was performed with SAS software (6.11 version, SAS Institute, North Carolina, USA). A value of p less than 0.05 was considered to be the threshold for statistical significance.

Results

The enrolment period ranged from June 1997 to November 1998. Due to delay in patient recruitment, 114 patients were entered in the study (58 in group 1, 56 in group 2) instead of the 194 patients as initially calculated. Fifty-six patients in each group received at least one bolus of cisatracurium (safety population). Fifty-two patients in group 1 and 50 patients in group 2 were evaluated (intent-to-treat population) (Fig. 1). Recovery from curarization was evaluated in 45 and 47 patients, respectively, in groups 1 and 2. Demographic characteristics, SAPS II scores at baseline, origin of respiratory distress and concomitant infused anesthetic drugs were comparable between the two groups (Table 1). Patients gas exchanges at the time of inclusion were similar in the two groups (Table 2). Expired tidal volumes (ml kg^{-1}) and PEEP levels (cmH_2O) were, respectively, [mean (SD)] 8.3 (2.1) and 7.5 (3.3) in group 1 and 8.1 (1.7) and 7.4 (4.2) in group 2.

Table 2 Gas exchange parameters in the intent-to-treat population at the time of inclusion in the study. All values are means (SD) (*TOF* train-of-four, *SD* standard deviation)

	Group 1 (TOF =0/4)	Group 2 (TOF =2/4)
PaO_2 (mmHg)	97.4 (25)	93.4 (28)
PaO_2/FIO_2	126 (33)	134 (40)
$PaCO_2$ (mmHg)	44.9 (12)	45.2 (11)
pH	7.35 (0.1)	7.37 (0.1)

Data concerning the cisatracurium doses infused, monitoring of neuromuscular function and recovery from neuromuscular blockade are summarized in Table 3. No statistically significant correlation was observed between the duration of cisatracurium infusion and delay to recovery from neuromuscular blockade.

Time courses of respiratory parameters

Nineteen patients (37%) in group 1 and 25 patients (50%) in group 2 had decreases in Pplat between the be-

Table 3 Cisatracurium infused doses, monitoring of neuromuscular function and recovery from neuromuscular blockade. Results are expressed as median (minimum-maximum) (*TOF* train-of-four, *PTC* post-tetanic count)

	Group 1 (TOF =0/4)	Group 2 (TOF =2/4)
Total duration of cisatracurium infusion (h)	28.9 (3.1–219.7)	31.4 (1.6–650.6)
Cisatracurium infusion rate during the study period (μg kg^{-1} min^{-1})	5.2 (2.1–13.7)	3.6 (1–13.5)
Cisatracurium infusion rate during the evaluation period (μg kg^{-1} min^{-1})	5.8 (3–15)	3.2 (0.8–14.9)
Average response to TOF stimulation during the evaluation period	0 (0.0–3.5)	2 (0.0–3.8)
Average response to PTC during the evaluation period	1 (0–8)	–
Number of changes in cisatracurium infusion rate during the evaluation period	0 (0–5)	3 (0–7)
Average response to TOF stimulation during the follow-up period	0 (0.0–0.2)	2.4 (0.0–4)
Delay to recovery from neuromuscular blockade (h)	1.25 (0.5–6)	0.75* (0.0–3.0)

* Statistically different from group 1 (p=0.0008, Wilcoxon, Mann and Whitney)

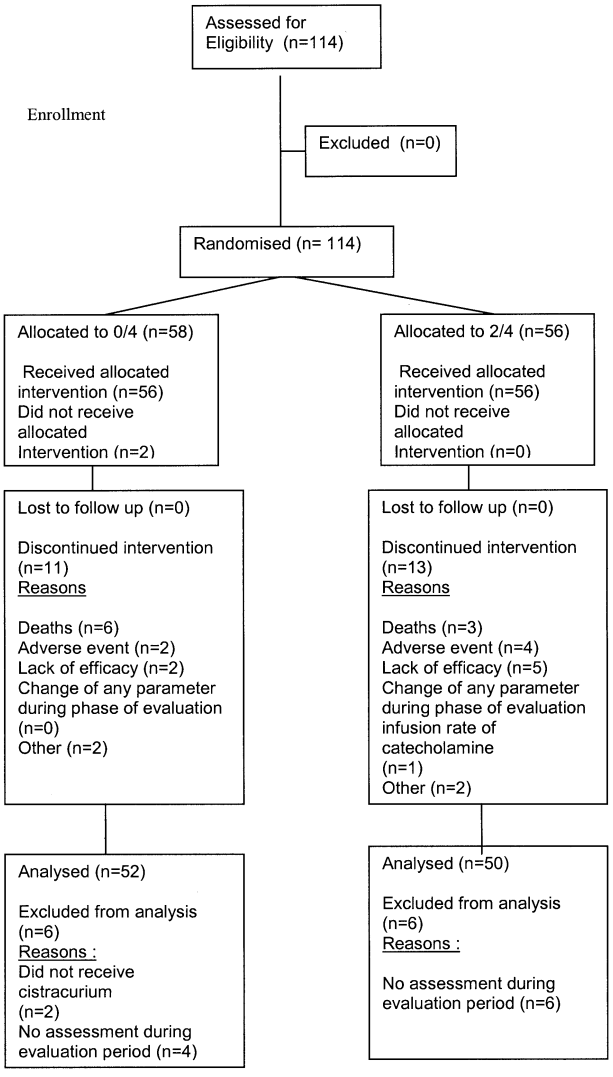

Fig. 1 Consort diagram showing the flow of participants through each stage of the randomized trial

ginning and the end of the evaluation period (chi-squared test, p=0.17). Time courses of respiratory parameters during the evaluation period are summarized in Table 4. A significant time effect for PaO_2/FIO_2 and Pplat values during the evaluation period was observed in both groups. In each group, the mean PaO_2/FIO_2 and Pplat values were significantly different at T0 and T2 h compared with the values before cisatracurium infusion; but did not differ between T0 and T2 h. No group effect (influence of depth of blockade) was observed for PaO_2/FIO_2 or Pplat time courses.

Hemodynamic stability, adverse effects

Hemodynamic parameters remained stable during the evaluation period in both groups (Table 5). The incidences of adverse events in the two treatment groups are summarized in Table 6. There was no statistically significant difference in the incidence of adverse events between the two groups. Adverse events possibly related to cisatracurium infusion were cardiac rhythm disorders in one patient and cutaneous eruptions in others. The incidence of mortality in the safety population was 46%, with no significant difference between the two groups (46% and 45% in groups 1 and 2, respectively). In the intent-to-treat population, 45 patients (44%) died: 7 (13%) and 3 (6%) patients, respectively, in groups 1 and 2 during the study period, 16 (31%) and 19 (38%) patients, respectively, after discharge from the trial. Death was considered by investigators as possibly related to the study treatment in one patient of group 2 (ventricular rhythm disorder). The data of the patients who died were analyzed in the intent-to-treat population.

Discussion

This study suggests that when a prolonged neuromuscular blockade is used in a mechanically ventilated patient in the expectation of improving respiratory function, aiming to maintain a depth of blockade at 2/4 responses

Table 4 Respiratory parameters before cisatracurium infusion, immediately after the start of the evaluation period (T0) and 2 h after TOF stimulation end points had been attained (T2 h) (*TOF* train-of-four, *Pplat* end inspiratory plateau airway pressure, PaO_2/FIO_2 ratio between arterial oxygen tension and inspired oxygen tension, $PaCO_2$ arterial partial pressure of carbon dioxide)

	Group 1 (Target TOF =0/4)			Group 2 (Target TOF =2/4)			*p* value (Repeated measures ANOVA)		
	Before infusion	T0	T2 h	Before infusion	T0	T2 h	T0 versus before infusion	T2 h versus before Infusion	T2 h versus T0
Pplat (cmH_2O; mean (SD))	29.1 (8.9)	28.5 (8.9)	28.5 (8.8)	27.7 (7.5)	26.4 (7.3)	26.6 (7.6)	0.0072	0.0164	NS
PaO_2/FIO_2 (mean (SD))	126 (33)	136 (50)	141 (55)	134 (40)	152 (50)	152 (52)	0.0018	0.0014	NS
$PaCO_2$ (mmHg; mean (SD))	44.9 (12.3)	45.2 (13)	44.6 (12.4)	45.2 (11.2)	44.3 (10.3)	43.4 (9.4)	NS	NS	NS
pH (mean (SD))	7.40 (0.1)	7.35 (0.1)	7.40 (0.1)	7.40 (0.1)	7.37 (0.09)	7.40 (0.1)	NS	NS	NS

Table 5 Hemodynamic parameters during cisatracurium infusion (*TOF* train-of-four, *SD* standard deviation)

	Group 1 (target TOF =0/4)		Group 2 (target TOF =2/4)	
	Before infusion (*n*=56)	During evaluation period (*n*=52)	Before infusion (*n*=56)	During evaluation period (*n*=52)
Systolic arterial pressure (mmHg; mean (SD))	122 (21)	126 (25)	124 (20)	124 (19)
Diastolic arterial pressure (mmHg; mean (SD))	60 (14)	60 (13)	61 (13)	61 (14)
Mean arterial pressure (mmHg; mean (SD))	81 (15)	82 (16)	82 (15)	82 (15)
Heart rate (beats min^{-1}; mean (SD))	99 (22)	101 (21)	101 (21)	100 (23)

Table 6 Incidence of adverse events during and after treatment in safety population (*TOF* train-of-four)

	Group 1 (*n*=56, TOF =0/4)		Group 2 (*n*=56, TOF =2/4)	
	Number of events	Number of patients	Number of events	Number of patients
All adverse events	21	16 (29%)	24	16 (29%)
Drug-related adverse events	4	3 (5%)	8	7 (13%)
Serious adverse events	12	8 (14%)	6	5 (9%)
Maximum intensity of drug-related adverse events				
Moderate		1 (2%)		2 (4%)
Severe		1 (2%)		2 (4%)
Serious drug-related adverse events	0	1 (2%)	0	0 (0%)
Pneumothorax		0 (0%)		1 (2%)

at TOF at orbicularis oculi provided similar effects on time courses of PaO_2/FIO_2 and Pplat as aiming to maintain a depth of blockade at 0/4 at orbicularis oculi. Such an intermediate level of neuromuscular blockade allowed a decrease in the total amount of the neuromuscular blocking agent infused, and a shorter delay for recovery from muscle paralysis after cessation of infusion.

This study was not designed to prove some beneficial effects of continuous neuromuscular blockade in the ICU setting. Such a study should have considered a control group of patients without neuromuscular blocking agent in order to appreciate spontaneous time courses of the recorded respiratory parameters. Consequently, clinical interpretation of the time courses of respiratory parameters in each group (significant, but hardly clinically relevant) would be highly hazardous. Recorded respiratory parameters were selected since it is suspected that they are influenced by continuous neuromuscular blockade [3, 8, 9, 10]. Therefore, the rationale for using continuous neuromuscular blockade in severe ICU patients remains to be demonstrated. Although some beneficial effects are expected, some related adverse effects are considered likely, such as unrecognized partial consciousness during paralysis, acquired neuromuscular disorders or prolongation of weaning from the ventilator [11]. Neither previously published studies nor the present study were designed to evaluate the benefit-risk ratio of this treatment. Consequently, continuous neuromuscu-

lar blockade should concern a minority of severe ICU patients at present, and should be maintained for as short a time as possible, as recommended [11].

The choice of orbicularis oculi for neuromuscular function monitoring was deliberate, although possibly considered to be a limitation of the study at first sight. The risk of measuring TOF responses at orbicularis oculi was effectively to stimulate the muscle directly, thus to underestimate the real depth of neuromuscular blockade in group 2 [12]. This may in part explain the absence of difference between the two groups. However, in patients synchronized to their ventilator, beneficial effects of neuromuscular blockade on respiratory function may be partly linked, although not demonstrated, to the depth of respiratory muscles paralysis [2, 3]. By increasing global thoraco-pulmonary static compliance, a deeper respiratory muscle paralysis could decrease Pplat and increase end-expiratory lung volume [9]. An increase in end-expiratory lung volume could decrease intra-pulmonary shunt and thus increase arterial oxygenation. The orbicularis oculi was therefore monitored because it has been proved to correlate with respiratory muscle paralysis better than the adductor pollicis in anesthetized patients [13, 14]. We hypothesized that the relative behaviors of orbicularis oculi, adductor pollicis and respiratory muscles in critically ill patients were similar to those in anesthetized patients, which has recently been partially confirmed [15]. In order to minimize misinterpretation of TOF responses, monitoring was cautiously performed by physicians who were used to monitoring neuromuscular function and who were unaware of the treatment group allocated.

One might consider that two deep levels of neuromuscular blockade (0 and 2/4 responses at orbicularis oculi) were compared, possibly explaining the absence of difference between the two groups. In this regard, initially we thought of comparing the two following depths of blockade: 2/4 responses to TOF stimulation at orbicularis oculi versus 2/4 responses to TOF stimulation at the adductor pollicis. However, the pre-cited study which compared the relative behaviors of orbicularis oculi and adductor pollicis in ICU patients had not been published at the time of study conception. We thus thought that conclusions based upon such a protocol could be open to criticism.

The main limitation of the study was the absence of standardization of the inspiratory hold for measurement of Pplat. A plateau may or may not exist in such patients and may need time to be established. Therefore, the lack of standardized duration of the pause can generate fluctuations of Pplat of ±1 cmH_2O, making the interpretation of Pplat variations, which were very mild, questionable.

The absence of difference between the two groups regarding percentages of patients with decreased Pplat at the end of the evaluation period can not be interpreted since the study power was insufficient. However, among the 102 patients analyzed, a higher percentage of patients with a decrease in Pplat was observed in group 2, which, of course, made an inverse significant result following inclusion of the statistically required number of patients possible, but unlikely. Conversely, statistically significant time effects were observed on the time courses of Pplat and PaO_2/FIO_2 during the evaluation period, allowing analysis of group effects, which were not statistically significant. Such an absence of difference between the two groups might be surprising at first sight. One hypothesis could be that continuous neuromuscular blockade has little effect on respiratory parameters, whatever the depth of blockade! This point has been previously discussed and outlines the usefulness of further studies aiming to investigate this central question.

Another hypothesis could concern concomitant sedation. A deep level of sedation was instilled before cisatracurium infusion in both groups. This sedation could have decreased oxygen consumption and thus increased arterial oxygenation [16]. Dosages of sedative drugs as well as Ramsay scores were similar in the groups. However, although useful in routine practice, such criteria were not validated for an accurate assessment of depth of sedation in ICU [17, 18]. The Sedation-Agitation-Scale, which is now valid in ICU patients, was not published at the time the study was undertaken [19]. A deeper sedation of patients in group 2 can therefore not be ruled out and may have distorted the study results.

The relatively short delay for recovery from neuromuscular blockade in both groups, which was independent of the duration of cisatracurium infusion, was in agreement with previously published data with cisatracurium [20, 21]. Aiming to maintain an intermediate level of blockade could shorten this delay, which was not surprising, of course. However, some patients in group 2 had four responses at TOF just before cessation of infusion. The difference observed in delay in recovery between the two groups was therefore possibly artificially increased. On the other hand, it suggests that maintenance of an accurate intermediate depth of neuromuscular blockade was difficult and that TOF monitoring should be used more than twice a day in order to adjust the rate of infusion.

The difference observed in the doses administered in the study by Prielipp et al. and the present study may appear surprising at first sight [20]. This difference can be mainly explained by the choice of the muscle group for neuromuscular function monitoring. In the study by Prielipp et al. the end point of blockade was controlled at adductor pollicis, instead of orbicularis oculi as in our study. Since orbicularis oculi seems more resistant to neuromuscular blocking agents than adductor pollicis, in ICU patients as in anesthetic patients [15], higher doses may be required. However, direct stimulation of orbicularis oculi may have occurred as previously discussed, which may have led to an underestimation of the depth

of blockade and thus to an artificial increase in the doses of cisatracurium required.

In summary, our data suggest that, in ICU patients receiving a prolonged neuromuscular blockade because of respiratory failure, the time courses of respiratory parameters (Pplat, PaO_2/FIO_2) were equivalent under a deep and an intermediate continuous neuromuscular blockade. Aiming to maintain an intermediate level of muscle paralysis, although requiring more frequent assessments of responses to TOF stimulation, could decrease the total amount of drug infused and allow a more rapid recovery from neuromuscular blockade following the discontinuation of infusion.

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