Background  The duration of action of neuromuscular blocking drugs (NBDs) varies between individuals and even within individuals in different settings.

Objectives  To define predictors of variance in duration of action of rocuronium and cisatracurium administered long-term.

Methods  A prospective, double-blind, multicenter trial that included 113 patients scheduled for major abdominal surgery and postoperative admission to the intensive care unit. Patients received repetitive (median, 7) equipotent doses of rocuronium or cisatracurium to maintain deep relaxation (twitch height of the adductor pollicis muscle <25% of baseline). Effects of weight, age, sex, American Society of Anesthesiologists risk score, lowest core temperature, duration of NBD administration, and tobacco smoking history on duration of action of cisatracurium and rocuronium were determined via multiple regression analysis.

Results  Only duration of NBD administration was predictive of the duration of action of rocuronium. The predicted increase in time to recovery of the train-of-4 ratio to 0.9 (duration TOF 0.9) per hour of continuous NBD treatment was 12.4 minutes. In contrast, only lowest core body temperature was predictive of cisatracurium's duration of action, and the predicted increase in duration TOF 0.9 per degree Celsius decrease was 9.8 min.

Conclusion  Duration of NBD treatment is strongly predictive of the duration of action of rocuronium, and body temperature is predictive of the duration of action of cisatracurium. These data may help decrease the incidence of drug-induced muscle weakness in recovery rooms and surgical intensive care units, particularly if neuromuscular transmission monitoring is not available. (American Journal of Critical Care. 2009;18:439-445)
Neuromuscular blocking drugs (NBDs) are commonly used in anesthesia and to treat critically ill patients in intensive care units (ICUs), but few clinicians use neuromuscular transmission monitoring. In the United Kingdom, 31% of critically ill children are likely to receive NBDs, but the depth of the blockade is routinely assessed in only 16% of patients. Results of a recent survey indicated that only 22% of Canadian ICUs use standardized protocols for NBD application and that 16% of all Canadian intensive care providers do not use neuromuscular transmission monitoring at all. Absence of neuromuscular transmission monitoring during repetitive administration of NBDs may be a patient safety issue, because partial paralysis is difficult to detect without neuromuscular transmission monitoring and has been known to persist more than 72 h in critically ill patients.

Uncontrolled neuromuscular blockade may increase the morbidity of critically ill patients. In fact, even a minimal degree of partial paralysis that cannot be detected without quantitative neuromuscular transmission monitoring (train-of-4 ratio, 0.5-1.0) can put a patient with an unsecured upper airway at risk of severe respiratory complications such as upper airway obstruction. Moreover, long-term administration of NBDs is a risk factor for the development of critical illness polyneuropathy. Finally, recent animal data suggest that a constant neuromuscular blockade with rocuronium and cisatracurium over only a single day evokes a myopathy that significantly decreases diaphragmatic force.

Therefore, we feel it is important for clinicians to get information about variables that predict the duration of action of NBDs administered long-term. We aimed at determining predictors of duration of action of cisatracurium and rocuronium administered long-term. Both of these NBDs are often used in anesthesia and intensive care medicine. On the basis of published data, we thought that weight, age, sex, American Society of Anesthesiologists (ASA) risk score, blood loss (suggesting instability of cardiac output), lowest core body temperature, duration of NBD administration, and tobacco smoking history might contribute to the variance in the mean duration of action of cisatracurium and rocuronium.

Methods

This randomized, double blinded, multicenter trial was performed at 5 German hospitals. After approval was gained from the local ethics committees, we evaluated 400 patients scheduled for major abdominal surgery of at least 3 hours’ duration and subsequent admission to an intensive care unit (Figure 1). Informed consent was obtained from 338 patients who met the preoperative inclusion criteria and did not have a history of neuromuscular, cardiovascular, pulmonary, or neurological disorder or acute renal or hepatic failure. Patients were then included if they met a final intraoperative inclusion criterion: intraoperative administration of at least 4 doses of NBD before admission to the ICU. Patients were randomly assigned to 2 groups to receive either rocuronium or cisatracurium.

Acceleromyography (TOF-Watch–SX Monitor, Organon Teknika, Eppelheim, Germany) of the adductor pollicis muscle was used to monitor neuromuscular transmission. After calibration of the device, the ulnar nerve was stimulated supramaximally
that a sample size of 100 patients would provide a total power of 90% to detect significant correlations between the variables.

All other comparisons were made with exploratory intent; no adjustment of the alpha error was made for multiple testing.

**Results**

This study included 338 patients from 5 hospitals who met the preoperative inclusion criteria. A total of 225 patients did not meet our intraoperative inclusion criterion; that is, they had not received at least 4 doses of NBD and been admitted to the surgical ICU after the surgery. Thus, data from 113 patients, who received a median of 7 repetitive doses of the respective NBD, were analyzed (Figure 1). The lowest core body temperature \( r = -0.44 \), blood loss \( r = 0.31 \), and duration of NBD administration \( r = 0.23 \) correlated significantly with the duration of action of cisatracurium at the predefined alpha error level of .15. In the rocuronium group, lowest body temperature \( r = -0.33 \), blood loss \( r = 0.43 \), duration of NBD administration \( r = 0.69 \), tobacco smoking history \( r = -0.28 \), and body weight \( r = 0.23 \) correlated with the duration of action at the predefined level. Subsequent multiple linear regression analysis revealed that the duration of rocuronium administration was predictive of its duration of action, but this was not the case for cisatracurium.

**Study Protocol**

On the morning of surgery, patients received 3.75 to 7.50 mg of midazolam for anxiolysis. Anesthesia was induced with 1.5 to 2.5 mg/kg propofol and 4 to 8 µg/kg fentanyl and maintained with propofol (5-10 mg/kg per hour) and remifentanil (0.05-2.00 µg/kg per minute). After loss of the corneal reflex, 0.1 mL/kg of the test drug (ie, cisatracurium 0.1 mg/kg or rocuronium 0.6 mg/kg) was administered to facilitate tracheal intubation. Whenever the single twitch height recovered \((T1/T0)\) to 25%, cisatracurium (0.025 mg/kg) or rocuronium (0.15 mg/kg) was given as a bolus dose. This procedure was repeated until the abdominal fascia had been completely closed. No NBD infusion had been given to any patient included in this study. The total dose was then calculated by the following formula: intubation dose + (standard repetitive dose \(\times\) number of repetition doses).

**Data Analysis**

On the basis of previous publications, we defined a priori the following variables that might influence the variance in duration of action of cisatracurium and rocuronium: weight, \(^{15,16}\) age, \(^{17}\) sex, \(^{18}\) ASA score, \(^{19}\) blood loss, \(^{20,21}\) lowest core body temperature, \(^{22}\) duration of NBD administration, \(^{23}\) and history of tobacco smoking. \(^{24-26}\) Variables that correlated significantly \((P = .15)\) with the mean dur 25 were included in our multiple regression analysis model, and an association of variables with the dur 25 of the respective NBD was assumed at a significance level of less than .05.

We conducted a separate power analysis for the 2 variables that showed the highest correlation with the dur 25 in our previous study for cisatracurium (ie, lowest body temperature, \( r = -0.44 \)) and rocuronium (ie, duration of NBD administration, \( r = 0.64 \)). To calculate the total power of our study, we multiplied the power values of each correlation and found that a sample size of 100 patients would provide a total power of 90% to detect significant correlations between the variables.
that only duration of NBD administration (mean [95% confidence interval, CI], 4.6 [3.6-5.3] h) is predictive of ($P<.001$) the duration of action of rocuronium and explains 44% of its variance. The dur 25 (mean [SD], 13.3 [4.1] min) was calculated to increase by 1.68 (95% CI, 0.60-2.76) min with each hour of NBD administration.

For cisatracurium, only lowest body temperature (mean [95% CI], 35.7°C [35.3°C-36.2°C]) is predictive of ($P<.005$) its duration of action and explains 17% of its variance. The dur 25 of cisatracurium increased by 2.4 (95% CI, 0.66-4.13) min per degree Celsius decrease in body temperature and had a mean (SD) of 15.1 (4.3) min (Figure 2).

We wondered whether the same variables that were predictive of the dur 25 would be predictive of the dur TOF 0.9, a variable that might be more clinically relevant. Linear regression revealed that duration of NBD administration is predictive of ($P<.001$) dur TOF 0.9 of rocuronium and explains 57% of its variance. The dur TOF 0.9 was calculated to increase by a mean of 12.4 (95% CI, 8.3-16.5) min per hour of NBD administration. In turn, lowest body temperature is predictive of ($P<.001$) dur TOF 0.9 of cisatracurium and explains 37% of its variance. The dur TOF 0.9 of cisatracurium increased by 9.8 (95% CI, 6.25-13.36) min per degree Celsius decrease in lowest body temperature (Figure 3).

**Discussion**

Results of this study show that the duration of action of cisatracurium and rocuronium administered long-term can be predicted by means of different variables. Duration of rocuronium’s effects increases with increasing duration of its administration, whereas the lowest body temperature is predictive of the duration of action of cisatracurium.

Rocuronium’s elimination half-life (83 min) is longer than that of cisatracurium (26 min). The differences in elimination half-life, however, do not necessarily translate into a longer duration of action of rocuronium if single doses or short-term infusions are given. Results of several studies indicate that the clinical durations of cisatracurium and rocuronium do not significantly differ under those conditions. Rocuronium is taken up by the liver and excreted into bile in high concentrations, and the major routes of elimination of unchanged rocuronium are in the feces and urine. Redistribu-
tion plays an important role as a patient recovers from rocuronium-induced neuromuscular blockade. In contrast, cisatracurium is removed by Hofmann elimination and has an intermediate clearance (0.3 L/kg per hour). These differences in elimination of NBDs may explain our observation that rocuronium’s duration of action increases with duration of its administration, whereas cisatracurium’s duration of action remains unchanged over time.

We thought that blood loss and hypothermia, conditions that affect hepatic function, would increase rocuronium’s duration of action. In fact, both variables correlated with the dur 25 of rocuronium.
we did not find a correlation of age with the duration of action of either of the 2 muscle relaxants we studied. Absence of a significant age effect may be explained by the relatively low age range of our patients, which in turn may reflect the typical age range of patients admitted to a surgical ICU.38,39 The patient’s sex also was not predictive of the duration of action of NBDs. In contrast, Xue et al18 reported a significantly longer duration of rocuronium in women than in men. This difference may be explained by the different mean age of the patients included in that study. The mean age of participants in the study by Xue et al was 30 years, whereas the mean age in our study was approximately 60 years. Thus it is likely that most of the women included in our study were postmenopausal, and the difference in sexual hormone levels between the participants in the 2 studies may explain the different results relating to steroid metabolism.40

The ASA physical status classification is a scoring system designed to stratify patients according to their perioperative risk. It is assigned either in the preoperative period or at the time of surgery by the anesthesiologist. The ASA classification score is included in the Department of Veterans Affairs National Surgical Quality Improvement Program database and is predictive of patients’ outcome after surgical procedures such as liver resection.41 However, we did not find evidence for the predictive value of the ASA risk score with

However, multiple regression analysis revealed that only the duration of NBD administration was an independent predictor of the duration of action of rocuronium. Thus, high blood loss and low core body temperature correlated with a longer duration of rocuronium are most likely epiphenomena of an increased duration of rocuronium administration, which was an independent predictor of the duration of rocuronium in the multivariate analysis. The increase in duration of action with time of administration may at least partially explain why the neuromuscular blockade effects of steroidal NBDs can last extremely long in critically ill patients.1

Cisatracurium is eliminated organ-independently by Hofmann degradation, which is dependent on temperature and pH. The influence of hypothermia on the time course of action of cisatracurium is in accordance with observations on cisatracurium’s effects during deep hypothermia for cardiac surgery.22,34 Our data support the view35 that body temperature already explains significant variation in cisatracurium’s duration of action when varied in a moderate temperature range that is likely to occur in intensive care patients.36,37 Moderate hypothermia may occur as a consequence of accidental or controlled intraoperative hypothermia, or hypothermia may even be applied as a neuroprotective treatment approach after cardiopulmonary resuscitation.36,37 Our data suggest that neuromuscular transmission monitoring is particularly important when cisatracurium is being used in critically ill patients with hypothermia.

Age is a factor that may influence the duration of action of steroidal muscle relaxants.17 However, we did not find a correlation of age with the duration of action of either of the 2 muscle relaxants we studied. Absence of a significant age effect may be explained by the relatively low age range of our patients, which in turn may reflect the typical age range of patients admitted to a surgical ICU.38,39 The patient’s sex also was not predictive of the duration of action of NBDs. In contrast, Xue et al18 reported a significantly longer duration of rocuronium in women than in men. This difference may be explained by the different mean age of the patients included in that study. The mean age of participants in the study by Xue et al was 30 years, whereas the mean age in our study was approximately 60 years. Thus it is likely that most of the women included in our study were postmenopausal, and the difference in sexual hormone levels between the participants in the 2 studies may explain the different results relating to steroid metabolism.40

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Figure 3 Individual mean values of the duration of recovery of the train-of-4 ratio to 90% after the last administration of a neuromuscular blocking drug (dur TOF 0.9) as a function of its predictors. A, Cisatracurium. Lowest core body temperature is predictive of dur TOF 0.9 of cisatracurium. B, Rocuronium. Duration of rocuronium administration is predictive of dur TOF 0.9 of the rocuronium.

Neuromuscular blocking drugs may cause polyneuropathy and myopathy.
respect to duration of action of NBD. Therefore, our data do not support the view that NBD dose should be decreased in patients with serious medical comorbid conditions.

In our study, a tobacco smoking history correlated with the duration of action of rocuronium, but smoking was not an independent predictor of rocuronium’s duration. The existing data on the effects of smoking on rocuronium’s effects are contradictory. Rautoma and Svartling reported a significantly increased requirement for rocuronium in smokers, and Reisli et al. reported a significantly longer duration in children with a history of exposure to second-hand smoke than in children without such exposure. Pühlinger et al. however, did not find any differences between tobacco smokers and nonsmokers in rocuronium’s onset time, peak neuromuscular blockade, and duration of action. Our findings indicate that tobacco smoking history is not an independent predictor of the duration of action of rocuronium, suggesting that the reported association between smoking and increased duration of action of rocuronium is not causative.

Muscle weakness is common in critically ill patients and may persist in a clinically relevant fashion even 1 year after patients’ hospital discharge. NBDs have been defined as a risk factor for critical illness polyneuropathy and myopathy, conditions manifested by muscle weakness in critically ill patients. Moreover, infusion of rocuronium and cisatracurium for a single day in rats compromises diaphragmatic function by a myopathic mechanism that does not involve neuromuscular transmission failure. Moreover, the combination of 18 to 69 hours of complete diaphragmatic inactivity and mechanical ventilation results in marked atrophy of myofibers in the diaphragm of humans.

Therefore, we advocate that all effort be made to avoid immobilizing patients unnecessarily by administering NBDs. If, however, NBDs are required in the ICU to protect a patient against the potential risk of high transpulmonary pressures they may generate, the dose should be titrated by means of neuromuscular transmission monitoring, taking into account that the duration of action varies from patient to patient, particularly during long-term administration. Quantitative neuromuscular transmission monitoring may be helpful in detecting an increased duration of action of NBD and consequently may even help clinicians reduce the incidence of muscle weakness in ICU patients.

We could not conduct a study directly in the ICU because it is very difficult to obtain informed consent from ICU patients. Furthermore, long-term administration of NBDs is rarely indicated in ICU patients. Therefore, we included patients scheduled for major abdominal surgery with subsequent admission to an ICU. Our patients did not have hepatic and renal dysfunction, conditions that will markedly influence the duration of rocuronium. We speculate that the association between the duration of rocuronium administration and its duration of action will be even stronger in patients with hepatic or renal failure.

In summary, our data show that core body temperature is an independent predictor of the duration of action of cisatracurium, whereas the duration of administration of rocuronium is predictive of the duration of action of rocuronium.

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REFERENCES

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Clinical Predictors of Duration of Action of Cisatracurium and Rocuronium Administered Long-Term
Philipp Fassbender, Götz Geldner, Manfred Blobner, Rainer Hofmockel, Christopher Rex, Shiva Gautam, Atul Malhotra and Matthias Eikermann

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