ORIGINAL ARTICLE

Effects of single-shot and steady-state propofol anaesthesia on rocuronium dose–response relationship: a randomised trial

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Conflicts of interest
Dr Christiane G. Stäuble has received honoraria and a travel grant from MSD Sharpe & Dohme. Dr Stefan Schaller holds stocks of the following companies in the healthcare sector in small amounts: Bayer AG, Siemens AG, GE, MERCK & CO INC, Rhoen-Klinikum AG and Fresenius SE. However, these holdings do not influence any decisions regarding the study. Dr Heidrun Fink has received honoraria and travel grants from the following companies: MSD Sharp & Dohme, Essex, Baxter, Care Fusion, GE Healthcare. Professor Manfred Blobner received honoraria and travel grants from MSD Sharp & Dohme and GlaxoSmithKline. Dr Roland Stäuble and Dr Christoph Unterbuchner have no conflicts of interest.

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Background: Similar to volatile anaesthetics, propofol may influence neuromuscular transmission. We hypothesised that the administration of propofol influenced the potency of rocuronium depending on the duration of the administration.

Methods: After consent, patients scheduled for elective surgery randomly received rocuronium either after induction of anaesthesia with propofol (2 min of propofol, $n = 36$) or after 30 min of propofol infusion (30 min of propofol, $n = 36$). Remifentanil was given in both groups. Neuromuscular monitoring was performed by calibrated electromyography. The dose–response relationship of rocuronium was determined with a single-bolus technique (0.07, 0.1, 0.15, 0.2, 0.3 and 0.45 mg/kg rocuronium). The primary endpoints were the ED_{50} and ED_{95} of rocuronium after 2 and 30 min propofol. Data are presented as means with (95% confidence interval). The trial is registered with the Eudra-CT: 2009-012815-16.

Results: A total of 72 patients were included. Time to maximal neuromuscular blockade was significantly shorter in patients after 30 min of propofol [3.3 min (2.9–3.7)] compared with patients anaesthetised with 2 min of propofol [4.6 min (4.0–5.2)]. After 30 min of propofol, the slope of the dose–response curve was significantly steeper (30 min of propofol: 4.34 [3.62–5.05]; 2 min of propofol: [3.34 (2.72–3.96)], resulting in lower ED_{95} values of rocuronium (30 min of propofol: 0.287 mg/kg [0.221–0.368]; 2 min of propofol [0.391 mg/kg (0.296–0.520)]. The ED_{50} were not different between groups.

Conclusion: The potency of rocuronium was significantly enhanced after propofol infusion for 30 min. Estimates of potency those are usually determined during steady-state anaesthesia might underestimate rocuronium requirements for endotracheal intubation at the time of induction.

Editorial comment: what this article tells us
The potency of rocuronium was significantly enhanced after 30 min of continuous propofol infusion prior to administration of rocuronium. Accordingly, lower ED_{95} values were found, and the time to maximum neuromuscular blockade by rocuronium was also shorter after 30 min of continuous propofol infusion.

The dose of neuromuscular blocking agents (NMBAs) recommended to facilitate tracheal intubation approximates at least two times the drug's effective dose ED_{95} (twice the dose required for a 95% effect).[1] This dose is administered to induce a very deep paralysis with a rapid onset of action providing acceptable intubating conditions within a reasonable time.[2,3] Dosage recommendations for NMBAs are usually based on dose–response studies performed in patients anaesthetised for 30–40 min prior to injection of the NMBA.[4,5] In this context, it is important to note that the time point of NMBA administration in those dose–response studies does not correlate with time point of NMBA administration in clinical practice. Here, the patient receives the NMBA at induction of anaesthesia shortly after a bolus of hypnotic is injected. Therefore, the dose relationship of NMBAs estimated during steady-state anaesthesia does not necessarily correlate with the dose–response curve at the time of induction.[6] Accordingly, a discrepancy between the applied dose of NMBA and the intubating conditions can become clinically apparent.

This might be related to effects of the co-administered anaesthetics at the neuromuscular junction.[7,8] It is well known that volatile anaesthetics augment the paralysing effects of non-depolarising NMBAs[4,9,10] depending on the duration of anaesthesia.[11–13] Consecutively, the international consensus guidelines (GCRP)[14] recommended to use intravenous instead of volatile anaesthetics for pharmacodynamic studies. However, at this time, the interactions of the intravenous anaesthetic propofol with the non-depolarising blocking agent rocuronium have not been investigated.

We hypothesised that the administration of propofol influences the potency of rocuronium dependent on the duration of its application. The objective of this study was to examine the dose requirements of rocuronium after 2 min of propofol anaesthesia, representing time of induction of anaesthesia, and after 30 min of continuous propofol anaesthesia, representing steady-state conditions. The primary endpoints were the ED_{50} and ED_{95} values of rocuronium determined after 2 min of propofol and after 30 min of propofol infusion. Secondary endpoints were the slopes of the dose–response curves and the onset time for maximal neuromuscular block.

Methods

Patients selection

This single centre, randomised, controlled double-blinded trial is registered at the European Clinical Trial Database with the EudraCT-number: 2009-012815-16 on 14 May 2009 and was approved by the ethics committee of the Faculty of Medicine at the Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany (protocol number: 2549/09) on 18 March 2010 and the Federal Institute for Drugs and Medical Devices ('Bundesanstalt für Arzneimittel und Medizinprodukte') on 8 August 2009 in Germany prior to patient enrolment. Patients were included if they were classed with physical status I and II according to the American Society of Anesthesiologists (ASA) classification, aged older than 18 years and scheduled for a surgical procedure under general anaesthesia.

Patients were excluded if they were expected to have a known or suspected difficult airway, a significant renal or hepatic dysfunction, a known neuromuscular disease, a known allergy to one of the drugs used in this study, a body mass index (> 30 mg/kg^2) or intake of any medication that might interact with muscle relaxants. Female patients were excluded if they were either pregnant, of childbearing potential or if they were breastfeeding.

Study design

Before the induction of anaesthesia, patients were randomly assigned to receive rocuronium either after 2 min of propofol infusion (group assignment: 2 min of propofol, $n = 36$) or after 30 min of continuous propofol infusion (group assignment: 30 min of propofol, $n = 36$; please see Fig. 1). Patients of the group 2 min of propofol ($n = 36$) received a single-shot propofol over 2 min, followed by injection of rocuronium. Patients of the group 30 min of propofol ($n = 36$) received a single-shot propofol followed by 30 min of continuous propofol infusion prior to administration of rocuronium. In both groups, remifentanil was supplemented for analgesia, once electromyography (EMG) was started. Airway was managed with laryngeal mask and/ or tracheal intubation according to the surgical procedure. In both groups, the dose–response relationship of rocuronium was determined with a single-bolus technique.[15] Therefore, patients were allocated to randomly receive 0.07, 0.1, 0.15, 0.2, 0.3 and 0.45 mg/kg rocuronium. The respective rocuronium drug dose was calculated according to the patient's actual body weight.[14]

The study was performed in blinded patients by two anaesthesiologists: one was blinded, the other one not. The not blinded anaesthesiologist ran the randomisation module, assigned the patients to the subgroups, and prepared the rocuronium dose in a covered syringe. The blinded anaesthesiologist noticed the propofol infusion protocol, but not the injected dose of rocuronium. The blinded anaesthesiologist performed anaesthesia, injected rocuronium in the covered syringe, and documented the EMG

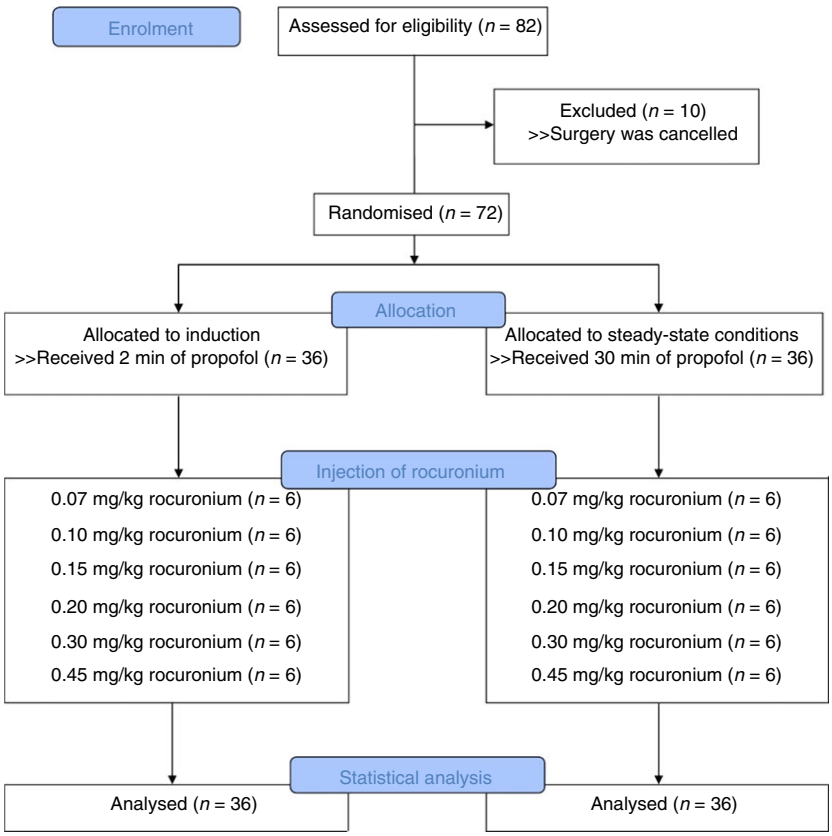

Fig. 1. CONSORT 2010 flow diagram. Initially, a total of 82 patients scheduled for elective surgical procedures have given written informed consent to participate in our study. Over the course of the study, 10 patients were excluded, because their surgical procedure had been cancelled. Therefore, a total of 72 patients were randomly allocated to receive rocuronium either after 2 min of propofol ($n = 36$) or after 30 min of propofol infusion ($n = 36$) and were included in our statistical analysis.

measures from the neuromuscular transmission module (m-NMT) in an S/5 GE Datex-Ohmeda Monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). After completion of the patient, the EMG variables were read out from the data sheet by the blinded anaesthesiologist. The group assignment was performed with a custom-made randomisation routine based on Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), which allows setting the number of groups, the number of cases per group, and in case of replacement of dropped-out patients if the case was performed per protocol.

Anaesthesia and neuromuscular monitoring

After arrival in the operating room, an intravenous line was placed into a forearm vein and an infusion of Ringer's lactate was administered. Standard anaesthesia monitoring including electrocardiography (lead II), non-invasive blood pressure and pulse oximetry was established. Oxygen was applied via facemask. For analgesia, an infusion with remifentanil (0.2 μg/kg/min) was started in both groups, when neuromuscular monitoring was set-up.

According to GCRP,[14] neuromuscular monitoring was performed using evoked EMG of the adductor pollicis muscle using the neuromuscular transmission module (m-NMT) in the S/5 GE Datex-Ohmeda Monitor. The forearm was immobilised, and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. Stimulation was started with the Train-of-Four (TOF) stimulation pattern. After at least 3 min of stable TOF stimulation, automatic calibration of the system was performed to find the individual supramaximal nerve stimulation at 20 s intervals.

Following calibration and stabilisation of the EMG for at least 20 min during remifentanil infusion (0.2 μg/kg/min), patients of the group 2 min of propofol received a bolus of propofol (2.5 mg/kg) over 2 min and were ventilated via face mask after loss of consciousness. Subsequently, each patient received the respective dose of rocuronium according to randomisation after which the degree of maximum neuromuscular block was measured (single-bolus method). In both experimental groups, six different doses of rocuronium (0.07, 0.1, 0.15, 0.2, 0.3 and 0.45 mg/kg rocuronium) were tested.

For patients with the group assignment 30 min of propofol, the study protocol was identical, except that patients were anaesthetised with an initial bolus of propofol (2.5 mg/kg) followed by 30 min of continuous propofol infusion (6 mg/kg/h) prior to administration of the respective dose of rocuronium. During propofol infusion, neuromuscular monitoring was set-up and started together with an infusion of remifentanil (0.2 μg/kg/min) for analgesia. Calibration and stabilisation of EMG were performed as described previously. After 30 min of continuous propofol infusion, the respective dose of rocuronium was injected according to randomisation, and the degree of maximum neuromuscular block was obtained.

In all patients, airway was managed with a laryngeal mask and/ or endotracheal intubation dependent on the respective surgical procedure and the anaesthesiologists' discretion. If endotracheal intubation was required, it was done after obtaining the study-related measurements. General anaesthesia was maintained with intravenous infusion of propofol (6 mg/kg/h) and remifentanil (0.2 μg/kg/min), while depth of hypnosis was continuously monitored with the GE Datex-Ohmeda Entropy Module (GE Healthcare, Milwaukee, WI, USA). To ensure haemodynamic stability during anaesthesia with propofol and remifentanil, vital parameters were continuously monitored. If required, fluids and norepinephrine were administered according to the anaesthesiologist's discretion.

Mechanical ventilation with oxygen in air (FiO_2 = 0.4) was adjusted to maintain an endtidal carbon dioxide tension between 34 and 38 mmHg. To assure metabolic stability, the patients' core temperature was controlled between 36°C and 37°C using a warm air blower.

Data management

Neuromuscular transmission and its suppression were described by parameters related to the TOF stimulation pattern, i.e. the responses to the four stimulations (T1, T2, T3 and T4) related to the baseline values. The ratio of the fourth twitch response (T4) to the first twitch response

(T1) is referred as TOF ratio. During calibration, the twitch height of the first twitch (T1) was adjusted to 100%.

Maximal neuromuscular blockade was defined as 100% minus the minimum of T1%. When the block was less than complete, time to maximum neuromuscular blockade was measured, i.e. the time elapsed between start of injection of the NMBA and the first of three consecutive T1s with the same or increasing amplitude.[14] If the neuromuscular blockade was complete, time to maximum neuromuscular blockade was not calculated.

Neuromuscular-monitoring data including T1% values, TOF ratio and time period from the start of injection of the NMBA, were continuously recorded on the S/5 GE Datex-Ohmeda Monitor and documented every 20 s by the blinded investigator in the patient's case report form. The anaesthesia record included detailed information about drug and fluid administration, systolic and diastolic arterial pressure, heart rate, end-tidal partial pressure of carbon dioxide, oxygen saturation, body temperature and Entropy (GE Healthcare) documented by the blinded anaesthesiologist.

Statistics

Assuming linear relation between the variables effect and dose by logit-transformation (effect) and logarithmic transformation (dose), 10 cases per tested factor (constant, dose, group, group × dose), i.e. 40 cases are appropriate to test our hypothesis. Additionally, it is postulated that the median dose has a 50% effect. Other approaches to calculate the sample size require information about the expected means and standard deviations of the variables, which are not available for this study. Own pilot studies suggested minimal differences. The GCRP guidelines ask for at least three dose groups.[14] To address this overall existing uncertainty, we decided to investigate six patients in each of the six dose groups.

The intention-to-treat population included all randomised patients who were scheduled for a surgical procedure. The per-protocol population included all patients who were actually operated at their scheduled appointment.

Assuming that the dose–response relation of the neuromuscular block and the rocuronium dose is governed by the Hill equation, linear regressions of the degree of block in logit scale (dependent factor), the respective dose of rocuronium in log scale, the experimental groups and their interaction (independent factor) were calculated. No and complete neuromuscular blockade (0% and 100%) cannot be transformed into logit scale. Accordingly, we replaced them by 0.005 and 0.995 respectively.[14]

The linear relations are characterised by slope (Hill coefficient) and intercept (mean, 95% confidence interval). The intercept (the calculated effect in logit scale when the logarithm of the dose is zero) and the slope, however, are abstract numbers (secondary endpoints). To allow a clinical interpretation, the linear regression is additionally described by specific doses together with their effect, e.g. the ED_{50} or ED_{95}. Simple retransformation allows constructing dose–response curves as well as calculating the groups' ED_{50} and ED_{95} and their 95% confidence intervals (primary endpoints).

All other data are presented as mean and 95% confidence interval and compared by Student's *t*-test.

Results

Data collection was performed from March 2012 up to January 2014. After written informed consent, 82 patients were enrolled. Ten patients were excluded, because their surgical procedure had been cancelled. Therefore, a total of 72 patients were analysed (Fig. 1). Patients' characteristics and data of airway management are shown in Table 1. Haemodynamic response and vasopressor administration before induction of anaesthesia and before injection of rocuronium are shown in Table 2.

If the rocuronium-induced block was less than complete, the mean time to maximal neuromuscular blockade was significantly lower in patients after 30 min of propofol infusion compared with patients anaesthetised with 2 min of propofol (Table 3). After 30 min of propofol infusion, the slope of the dose–response curve was significantly increased when compared with the slope of the dose–response curve after 2 min of propofol, resulting in lower ED_{95} values during steady-state conditions (Fig. 2

Table 1 Patients' characteristics: values are given in means and 95% confidence intervals (95% CI).

	2 min of propofol (n = 36)	30 min of propofol (n = 36)
Age (years)	46.9 (22.8–71.1)	52.3 (25.9–78.7)
Body mass index (kg/m^2)	24.5 (23.3–25.8)	25.8 (24.5–26.9)
Body height (m)	1.73 (1.70–1.76)	1.78 (1.75–1.82)
Body weight (kg)	73.4 (68.6–78.8)	82.0 (77.4–86.7)
Gender	26 Male/10 female	30 Male/6 female
Patients per American Society of Anesthesiologists class I/II	27/9	20/16
Airway management		
Laryngeal mask	5/36	22/36
Endotracheal intubation	31/36	14/36

Table 2 Patients' haemodynamics: values are given in means and 95% confidence intervals (95% CI).

	2 min of propofol (n = 36)	30 min of propofol (n = 36)
Before induction of anaesthesia		
Mean arterial pressure (mmHg)	98.7 (94.9–102.9)	104.8 (101.5–107.9)
Heart rate (beats/min)	76 (71–80)	77 (71–81)
Vasopressor administration (10 μg Norepinephrine i.v.)	0/36 patients	0/36 patients
Before injection of rocuronium		
Mean arterial pressure (mmHg)	79.7 (75.8–83.6)	78.2 (75.8–81.1)
Heart rate (beats/min)	67 (62–72)	60 (56–64)
Vasopressor administration (10 μg Norepinephrine i.v.)	3/36 patients	3/36 patients

and Table 4). In contrast, the ED_{50} values were comparable (Table 4).

Discussion

This study demonstrated that potency of rocuronium is significantly enhanced after 30 min of continuous propofol infusion. In addition, time to maximum neuromuscular blockade by rocuronium was shorter during steady-state conditions of propofol.

Since it was generally agreed that intravenous anaesthetic agents do not potentiate the paralysing effects of NMBAs, there are only two clinical studies investigating the impact of the duration of intravenous anaesthesia on neuromuscular blockade.[5,16] Plaud et al. compared the onset time and the depth of neuromuscular blockade by mivacurium at induction of anaesthesia and after 15 min of propofol anaesthesia.[5] Since only the sub-paralytic dose of 0.1 mg/kg mivacurium was investigated, the authors clearly proved that the effect of this specific dose is enhanced after 15 min of propofol anaesthesia, but could not provide any information about the interaction between propofol and mivacurium. Another study focussed on the dose–effect relation of mivacurium dependent on the duration of propofol infusion monitored by phonemyography.[16] The potency of mivacurium was significantly increased (approximately 1.5-fold) after total intravenous anaesthesia (TIVA) with propofol for 20 min compared with 5 min.[16] So far, those results have not been confirmed for other NMBAs, e.g. rocuronium. Therefore, it is interesting to note that our data support these findings.[16]

The effects of NMBAs depend on the acetylcholine receptor number (nAChR) at the neuromuscular junction, the concentration of the respective NMBA and the affinity of the NMBA for the receptor.[17] An alteration in the density of nAChRs typically results in a parallel shift of the dose–response curve, i.e. in a change of the intercept with unchanged slope. An alteration in the binding affinity between receptors and NMBA results in a changed slope, whereas changes in the intercept cannot be interpreted any longer.[17] Therefore, the higher slope after 30 min of propofol infusion suggests an increased affinity of rocuronium for the receptor during steady-state conditions. Interestingly, this finding correlates with a previous observation, where the increased potency of non-depolarising NMBAs seen during anaesthesia with volatile anaesthetics was attributed to an enhanced NMBA affinity at the receptor site.[18]

Healthy humans typically present a slope of 3.5–5.0, irrespectively, of the NMBA.[19] The slope of 4.34 (3.62–5.05) seen after 30 min of propofol in this study is consistent with previ-

Table 3 Time to maximal neuromuscular blockade (onset max): values are given in means and 95% confidence intervals (95% CI).

	Rocuronium (mg/kg)	2 min of propofol Mean (95% CI) (min)		30 min of propofol Mean (95% CI) (min)		Mean difference (min) (95% CI)	
Onset max (min)	0.07	4.8 (2.7–6.9)	(n = 6)	3.1 (2.3–4.0)	(n = 6)	1.6 (−0.9 to 4.2)	
	0.1	3.4 (2.6–4.1)	(n = 6)	2.5 (1.8–3.2)	(n = 6)	0.9 (−0.3 to 2)	
	0.15	3.9 (3.1–4.7)	(n = 6)	3.5 (2.7–4.4)	(n = 6)	0.4 (−0.9 to 1.7)	
	0.2	5.1 (4.0–6.3)	(n = 6)	3.6 (2.7–4.4)	(n = 6)	1.6 (−0.1 to 3.2)	
	0.3	5.1 (3.5–6.8)	(n = 5)	4.4 (3.9–4.9)	(n = 3)	0.7 (−2 to 3.5)	
	0.45	6.1 (3.5–8.6)	(n = 3)	3.3 (NA)	(n = 1)	NA	
	All doses	4.6 (4.0–5.2)	(n = 32)	3.3 ± (2.9–3.7)	(n = 28)	1.3 (0.5–2)	P = 0.001

When the block was less than complete, time to maximum neuromuscular blockade was measured, i.e. the time elapsed between start of injection of the NMBA and the first of three consecutive T1s with the same or increasing amplitude.[14] If the neuromuscular blockade was complete, time to maximum neuromuscular blockade was not calculated.

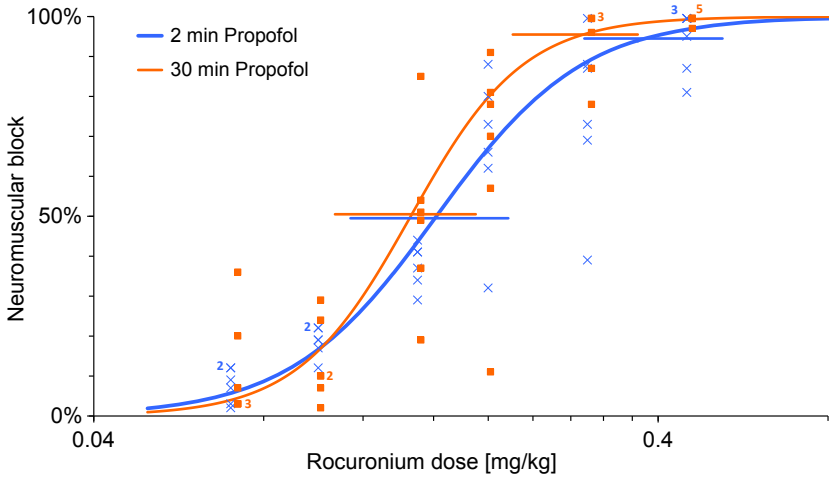

Fig. 2. Pharmacodynamics of rocuronium. The dose–response relationship of rocuronium in both groups (2 min of propofol or 30 min of propofol) was determined with a single-bolus technique (0.07, 0.1, 0.15, 0.2, 0.3 and 0.45 mg/kg rocuronium). After 30 min of propofol infusion, the slope of the dose–response curve was significantly increased when compared with the slope of the dose–response curve seen after 2 min of propofol. Consecutively, the ED_{95} of rocuronium was significantly decreased after 30 min of propofol. It is important to note that we had six subjects in each subgroup as also indicated in the CONSORT flow diagram (Fig. 1). Looking at our dose–response curves (Fig. 2), there are 12 data points at each dose on the dose–response curve. However, we had multiple data points at the same effect. To avoid misunderstanding, those data point are tagged with numbers indicating the individual number of data points at the same effect.

Table 4 Pharmacodynamics of rocuronium values are given in means and 95% confidence interval (95% CI).

	2 min of propofol Mean (95% CI)	30 min of propofol Mean (95% CI)	
Slope of dose–response curve	3.34 (2.72–3.96)	4.34 (3.62–5.05)	P = 0.037
Intercept of dose–response curve	6.09 (4.94–7.24)	8.35 (7.03–9.68)	P = 0.011
ED_{50} (mg/kg) of rocuronium	0.162 (0.114–0.217)	0.146 (0.107–0.190)	
ED_{95} (mg/kg) of rocuronium	0.391 (0.296–0.520)	0.287 (0.221–0.368)	

ous observations.[19] For clinical considerations, however, differences in slope as well as intercept are inessential, as long as they do not affect the dose recommendations, which are mainly based on the ED_{95} estimates. Therefore, it is important to note, that the significantly flatter slope of 3.34 (2.72–3.96) after 2 min of propofol infusion resulted in 36% higher ED_{95} values for the bolus-like setting.

There are many ED_{95} estimates of rocuronium from studies, in which propofol anaesthesia $\geq$ 20 min was used as control group, and those from other studies, in which propofol was given for $\leq$ 5 min, mainly in the context of other objectives. Multiple factors are known to influence the dose–response relationships for NMBAs such as the used method (single-dose vs. cumulative-dose technique), type and duration of anaesthesia, as well as the neuromuscular-monitoring technique. Therefore, the specific influence of the duration of propofol infusion might get lost in any comparison between different studies, even, in a thoroughly performed meta-analysis. Accordingly, we performed the presented comparative trial focussing just on the specific effect of propofol duration. Nevertheless, the lower ED_{95} of 0.287 mg/kg (0.221–0.368) after 30 min of propofol as well as the higher ED_{95} of 0.391 mg/kg (0.296–0.520) estimated during induction of anaesthesia are broadly consistent with previously published values.[4,20–24]

In clinical practice, not only the slope, but also the pharmacologically well-accepted ED_{50} is of little importance, because there are no dose recommendations for NMBAs based on these estimates. Therefore, the lack of major difference in ED_{50} values in this study has no direct clinical implication. Nevertheless, our ED_{50} estimates of 0.162 mg/kg (0.114–0.217) after 2 min of propofol and 0.146 mg/kg (0.107–0.190) after 30 min of propofol are in line with others published values.[4,22–25]

The time to maximum neuromuscular blockade[14] did not depend on the dose of rocuronium confirming previous findings.[26] In this study, the times to maximum blockade was shorter after 30 min compared with 2 min of propofol infusion. Beside an explanation of this difference due to neuromuscular reasons, haemodynamic effects must be considered, especially in case of rocuronium.[27,28] Propofol causes vasodilatation and myocardial depression.[29] For remifentanil, a previous study documented that its prior administration delays onset of rocuronium during TIVA most likely due to a decrease of cardiac output.[30] In this study, we did not measure cardiac output, but the haemodynamic response before induction of anaesthesia and before injection of rocuronium suggests similar haemodynamic conditions in both groups consisting of healthy patients (ASA I–II). In addition, we can also exclude any effect based on the co-administration of vasopressors,[27] since only 3 of 36 patients in each propofol group received a bolus of 10 μg norephinephrine before NMBA injection.

Although we did not investigate the mechanism behind our findings, the differences in the slope are in line with recent findings of basic research investigating direct effects of propofol at the neuromuscular junction. Three binding sites for propofol were identified in the Torpedo (muscle type) nAChR suggesting inhibitory effects.[7] In healthy adults, however, propofol alone did not decrease twitch tension.[31] A possible explanation for this might be the fact that impaired neuromuscular transmission can only be detected, if more than 75% of the nAChRs are occupied.[17] Moreover, propofol decreases muscle tone in the absence of NMBAs,[32] suggesting a peripheral effect at the muscle membrane.[33] To avoid these direct effects of propofol on muscle force, we *a priori* decided to use EMG.

Clinical implications for the anaesthesiologist

The potency of rocuronium is significantly enhanced after 30 min of propofol infusion. Therefore, the rocuronium ED_{95} values obtained during propofol infusion for 30 min underestimate the rocuronium requirements at the time of induction. In conclusion, our findings confirm the current recommendations to administer at least twice the ED_{95} of rocuronium for induction to completely paralyse patients.[1,2]

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. (Probit-analysis). Rocuronium requirements after 2 min and 30 min of propofol anaesthesia.
Table S1. Pharmacodynamics of rocuronium (probit-analysis) values are given in means and 95% confidence interval (95% CI).