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Influence of a continuous prednisolone medication on the time course of neuromuscular block of atracurium in patients with chronic inflammatory bowel disease

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Background. Corticosteroids interact with neuromuscular blocking agents. However, experimental data are contradictory: enhancement and attenuation of the neuromuscular block has been observed. This study tested the influence of long-term medication with prednisolone on atracurium-induced neuromuscular block.

Methods. Sixty patients with chronic inflammatory bowel disease undergoing elective abdominal surgery were investigated. Thirty patients received a long-term medication with prednisolone (Group A) and 30 were without corticoid medication (Group B). Additionally, another 30 patients without inflammatory bowel disease and without corticoid medication served as control (Group C). The following parameters of an atracurium-induced neuromuscular block (0.25 mg kg^{-1}) were measured: onset time, maximum block, recovery to 25% first twitch height, recovery index (time from 25% until 75% recovery of first twitch), duration to recovery to a train-of-four (TOF) rate of 0.7 and 0.9.

Results. The groups did not differ with regard to onset time, maximum block, and recovery index. The duration to 25% twitch height was significantly lower in Group A [18.1 (0–30.7) min] compared with Group B [23.5 (0–36.7) min; $P<0.05$]. Duration to a TOF rate of 0.7 and 0.9, respectively, were significantly reduced in Group A [36.1 (7.9) and 40.9 (9.0 min)] compared with Group B [47.9 (7.6) and 53.4 (9.2) min; $P<0.001$].

Conclusions. Long-term medication with prednisolone resulted in a shorter duration of an atracurium-induced neuromuscular block in patients with Crohn's disease or ulcerative colitis. The presence of the inflammatory bowel disease did not influence the time course of the neuromuscular block.

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Data on the influence of cortisone on the time course of neuromuscular blockade are contradictory and are obtained from experimental settings: while Kindler and colleagues,[1] Shima,[2] and Paradiso and colleagues[3] found an additive inhibition and prolongation of neuromuscular block, other authors described an increase in transmitter release,[4] improved muscle performance,[5] or prevention of neuromuscular block of prednisolone in an experimental model.[6] To date, clinical studies investigating this topic do not exist. Therefore, we performed the present study in order to investigate whether long-term administration of cortisone influenced the time course of the neuromuscular block after a single dose of atracurium in patients with Crohn's disease or ulcerative colitis.

As an inflammatory process itself might also be able to attenuate the intensity of the neuromuscular block,[7 8] the study design had to consider the influence of the underlying chronic inflammatory bowel disease.

Methods

Patients and methods

The study design was prospective, unblended, and monocentred. After obtaining approval from the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität zu Köln, University Hospital of Cologne, Germany), we included 90 patients aged 18–65 yr, American Society of Anesthesiologists Physical Status I or II, 50–100 kg body weight, undergoing elective abdominal surgery in general anaesthesia necessitating intraoperative neuromuscular block. Sixty patients were suffering from chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), 30 out of them taking a prednisolone medication for more than 4 weeks (Group A), the other 30 without anti-inflammatory medication (Group B). Thirty patients without chronic inflammatory disease and without cortisone medication served as control (Group C) and were matched to Groups A and B with regard to gender, age, height, and body weight.

C-reactive protein (CRP) was determined in all patients the day before surgery in order to detect differences between groups with regard to the inflammatory status.

Exclusion criteria were inflammatory disease other than Crohn's disease or ulcerative colitis, expected difficulties with tracheal intubation, risk of pulmonary aspiration, known allergies to the drugs tested, pregnancy, neuromuscular disorders, and intake of drugs affecting neuromuscular block, such as furosemide, magnesium, or cephalosporins, hepatic or renal insufficiency.

Induction and maintenance of anaesthesia

The patients were premedicated with lorazepam 1 mg orally. Anaesthesia was induced with continuous infusion of remifentanil 0.25 $\mu g\ kg^{-1}\ min^{-1}$, fentanyl 2–3 $\mu g\ kg^{-1}$, and propofol 2–3 $mg\ kg^{-1}\ h^{-1}$. The trachea was intubated without use of neuromuscular blocking agents and patients' lungs were ventilated to normocapnia (36–40 mm Hg) during the whole study period. Anaesthesia was maintained by continuous infusion of remifentanil 0.15–0.25 $\mu g\ kg\ min^{-1}$ and propofol 3–5 $mg\ kg\ h^{-1}$ (total i.v. anaesthesia). Haemodynamic parameters were maintained in a normal range ($\pm$20% of baseline values) by additional administration of propofol and remifentanil in case of tachycardia or arterial hypertension and injection of ephedrine or atropine in case of hypotension or bradycardia.

Core and surface temperature was measured and kept $>36^{\circ}C$ (nasal) and $34^{\circ}C$ (surface over musculus adductor pollicis), respectively, by a convective warming device (Bair Hugger® 505, Augustine Medical Inc., MN, USA).

Neuromuscular measurements

Neuromuscular transmission was assessed by electromyography (Relaxograph, Datex Instrumentarium Corporation, Helsinki, Finland) at the adductor pollicis muscle using transcutaneous Ag/AgCl electrodes. Measurements were started after induction of anaesthesia. The Relaxograph was set to deliver supramaximal train-of-four (TOF) stimuli (0.1 ms duration) at 2 Hz every 20 s. The first of the four responses was considered the twitch height (T_1). To minimize movement-induced changes in twitch response, the patient's hand was carefully fixed in a splint. After a 10 min period of stabilization and variation of the EMG response of $<2\%$ for at least 3 min, the Relaxograph was recalibrated and control T_1 was determined.

In all three groups, atracurium 0.25 $mg\ kg^{-1}$ ($1\times ED_{95}$) was injected over a period of 5 s and the i.v. line flushed with Ringer's solution. Afterwards, the following parameters were measured: maximum T_1 depression and onset time of neuromuscular block (time between the beginning of injection of atracurium and maximum T_1 depression); clinical duration (DUR 25%): time between administration of atracurium and recovery to 25% twitch height; recovery index: time interval from 25 to 75% twitch height recovery; duration TOF rate 0.7: time from injection of atracurium to a recovery of neuromuscular block to a TOF ratio of 0.7; duration TOF rate 0.9: time from injection of atracurium to a recovery of neuromuscular block to a TOF ratio of 0.9. Patients in whom twitch height did not recover to control values were excluded from the study.[9]

Statistical analysis

Normally, distributed data were compared by using the one-way analysis of variance, followed by the Tukey *post hoc* test for multiple comparisons (height, recovery index, TOF rate 0.7, TOF rate 0.9), not normally distributed data by the Kruskal–Wallis one way analysis of variance on ranks followed by Dunn's post-test for multiple comparisons (weight, age, CRP, maximum T_1 depression, onset time and clinical duration) and χ^2 test (gender). All tests were performed two-tailed with a significance level of $\alpha=0.05$ and $1-\beta=0.8$.

The sample size was calculated prospectively according to the following criteria: for a 90% power to detect a 10% difference (SD 8.5) in maximal neuromuscular block with $P=0.05$, 19 patients per group were needed.[10] Statistical analysis was performed using the software package Sigma Stat for Windows 2.03 (SPSS Inc., USA).

Results

Patient characteristics and dropouts

In 15 out of the 90 patients (three in Group A, six in Group B, and six in Group C) the measurements had to be terminated before the end of the observation period because a deep neuromuscular block was required intraoperatively. These patients received a second atracurium

Table 1 Patient characteristics. Group A: chronic inflammatory bowel disease with long-term prednisolone medication; Group B: chronic inflammatory bowel disease; no cortisone medication; Group C: control group. CRP: C-reactive protein. No significant differences between groups

	Gender (male/female), number	Age (yr), median (range)	Height (cm), mean (SD)	Weight (kg), median (range)	CRP (mg dl^{-1}), median (range)	Prednisolone (mg daily), mean (range)
Group A (n=27)	12/15	36.0 (23–65)	171.0 (7.5)	65.0 (50–97)	0.55 (0.5–7.7)	21.9 (5–75)
Group B (n=24)	11/13	39.0 (25–65)	169.9 (9.2)	67.5 (50–95)	0.5 (0.5–3.6)	–
Group C (n=24)	11/13	41.5 (18–62)	173.3 (9.5)	70.0 (55–95)	0.5 (0.5–3.1)	–

Table 2 Time course of the neuromuscular block in all patients. Onset time: time between the beginning of injection of atracurium and maximum T_1 depression; twitch height: twitch height in per cent compared with baseline values; duration: time between administration of atracurium and recovery to 25% twitch height; recovery index: time interval from 25 to 75% twitch height recovery; duration TOF rate 0.7: time from injection of atracurium to a recovery of neuromuscular block to a train-of-four (TOF) ratio of 0.7; duration TOF rate 0.9: time from injection of atracurium to a recovery of neuromuscular blockade to a TOF ratio of 0.9. *P<0.05 *vs* Group A; #P<0.001 *vs* Group A

	Onset time (s), median (range)	Twitch height (% T_1 height), median (range)	Duration (min), median (range)	Recovery index (min), mean (SD)	Duration TOFR 0.7 (min), mean (SD)	Duration TOFR 0.9 (min), mean (SD)
Group A: chronic inflammatory bowel disease with long-term prednisolone medication (n=27)	280 (180–480)	15.0 (0–60)	18.1 (0–30.7)	10.8 (3.5)	36.1 (7.9)	40.9 (9.0)
Group B: chronic inflammatory bowel disease; no cortisone medication (n=24)	260 (180–360)	9.5 (0–28)	23.5 (0–36.7)*	12.7 (4.0)	47.9 (7.6)#	53.4 (9.2)#
Group C: control group (n=24)	270 (160–460)	8.5 (0–52)	22.0 (0–39.7)	11.2 (3.6)	44.5 (9.1)	50.8 (10.5)

bolus after recovery to 25% twitch height and were therefore excluded from the study. Thus, the study population consisted of 75 patients.

Patient characteristics and preoperative CRP-values did not differ between the study groups. The patients in Group A received 21.9 (5–75) mg prednisolone daily. Details are summarized in Table 1.

Time course of neuromuscular block

Maximum T_1 depression and onset time of neuromuscular block were similar in all groups. With regard to the recovery index, no differences were observed between the groups (Table 2). In seven patients of Group A, one patient of Group B, and three patients of Group C, maximum T_1 depression did not decrease <25%. In these patients, the parameter clinical duration was assumed to be 0 and the recovery index was not analysed.

The clinical duration of atracurium in Group A was significantly shorter compared with Group B [18.1 (0–30.7) *vs* 23.5 (0–36.7) min; P<0.05]. The clinical duration in Group C reached 22.0 (0–39.7) min, but there was no significant difference between the clinical duration in Group C and the values obtained in Group B, respectively. The duration to a TOF rate of 0.7 was significantly reduced in Group A [36.1 (7.9) min] compared with Group B [47.9 (7.6) min; P<0.001].

The duration to a TOF rate of 0.9 in Group A was 40.9 (9.0) min. Again, this time interval was significantly shorter than in Group B [53.4 (9.2) min; P<0.001]. Details are summarized in Table 2.

A correlation between prednisolone dose and time course of the neuromuscular block was observed. The correlation coefficients were −0.57 and −0.51 for the duration to a TOF rate of 0.7 and 0.9, respectively, (P<0.0001). Data are presented in Figure 1.

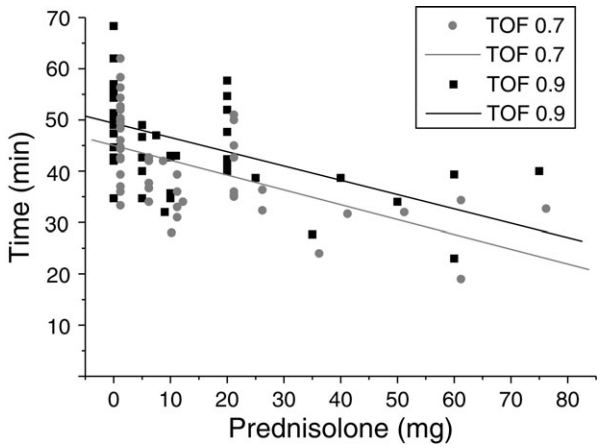

Fig 1 Influence of prednisolone dose and recovery from the neuromuscular block. Correlation coefficient: −0.57 for TOF 0.7 and −0.51 for TOF 0.9 (P<0.0001).

Thirteen patients in Group A, two patients in Group B, and two patients in Group C had elevated CRP-values (>0.5 mg dl^{-1}). In order to detect a possible influence of the CRP-value on the measurements, a second statistical analysis including only patients with a CRP of <0.5 mg dl^{-1} was performed. The results were similar to the data documented for all patients and are presented in Table 3. The duration to a TOF rate of 0.7 was shorter in Group A [34.8 (8.9) min] compared with Group B [48.3 (7.4) min; P<0.05]. Recovery to a TOF rate of 0.9 was faster in Group A [39.4 (10.2) min] than in Group B [54.0 (9.2) min; P<0.05].

Table 3 Time course of the neuromuscular block in patients with CRP-values <0.5 mg dl^{-1}. Onset time: time between the beginning of injection of atracurium and maximum T_1 depression; twitch height: twitch height in per cent compared with baseline values; duration: time between administration of atracurium and recovery to 25% twitch height; recovery index: time interval from 25 to 75% twitch height recovery; duration TOF rate 0.7: time from injection of atracurium to a recovery of neuromuscular block to a TOF ratio of 0.7; duration TOF rate 0.9: time from injection of atracurium to a recovery of neuromuscular block to a TOF ratio of 0.9. *P<0.05 *vs* Group A

	Onset time (s), median (range)	Twitch height (% T_1 height), median (range)	Duration (min), median (range)	Recovery index (min), mean (SD)	Duration TOFR 0.7 (min), mean (SD)	Duration TOFR 0.9 (min), mean (SD)
Group A: chronic inflammatory bowel disease with long term prednisolone medication (n=14)	260 (180–420)	11.0 (0–60)	18.7 (0–30.7)	10.0 (3.5)	34.8 (8.9)	39.4 (10.2)
Group B: chronic inflammatory bowel disease; no cortisone medication (n=22)	240 (180–360)	9.0 (0–28)	22.8 (0–36.7)	11.9 (3.9)	48.3* (7.4)	54.0* (9.2)
Group C: control group (n=22)	280 (160–460)	10.0 (0–52)	22.0 (0–39.7)	11.8 (3.6)	47.1 (9.4)	53.7 (10.8)

Discussion

There are two major results of this study: (i) long-term medication with prednisolone shortened the duration of an atracurium-induced neuromuscular block by ~20%. (ii) The presence of Crohn's disease or ulcerative colitis did not influence the time course of the neuromuscular block. These findings might be of interest for all anaesthesiologists treating patients taking prednisolone, suffering from one of the diseases mentioned above, or both.

In the experimental setting, prednisolone reduced the effectiveness of neuromuscular blockers.[6] Of note, betamethasone was also able to induce a resistance to neuromuscular block in rat hemidiaphragm preparations.[11] Therefore, the interaction between corticoids and neuromuscular blocking agents does not seem to be limited to prednisolone, but might be characteristic for all corticosteroids.

Although the mechanism is not fully understood, several possible sites of interaction of steroids with neuromuscular transmission have been suggested: (i) glucocorticoids have been shown to possess a direct facilitatory effect at the impulse generating end of the motor nerve axon;[12] (ii) corticosteroids act presynaptically stimulating synthesis,[13] spontaneous release,[14] and stimulated release of acetylcholine;[15] (iii) however, at large concentrations, corticosteroids might possess a post-synaptic depressant effect on neuromuscular transmission.[16]

However, these experimental studies refer to acute administration of corticosteroids. In contrast, the patients in our study took a long-term medication over a period of several weeks or more.

To date, clinical investigations referring to the influence of corticoids on the time course of neuromuscular blocking agents focused on Intensive Care Unit patients. In this group of patients, administration of corticosteroids in combination with neuromuscular blocking agents seems to be associated with acute myopathy and prolonged weakness.[17–20] With regard to these data, our results presenting an accelerated recovery from neuromuscular block in patients receiving prednisolone are quite surprising. One explanation might be that we investigated a completely different group of patients in the present study (i.e. American Society of Anesthesiologists Physical Status I or II, scheduled for elective surgery). Therefore, our patients were not at risk of developing a critical illness neuropathy or myopathy and did not suffer from life-threatening diseases or severe trauma.

An acute infection or even sepsis as a reason for the attenuation of the neuromuscular block in the group of patients receiving prednisolone can be ruled out since emergency cases were excluded from the study and CRP values did not differ significantly between the three study groups.[8]

Additionally, the results in the subgroups of patients with CRP-values <0.5 mg dl^{-1} were similar to the data documented in all patients.

With regard to onset time and maximum T_1 depression, the groups did not differ significantly from each other. This might relate to the fact that we administered an atracurium bolus leading to a 95% neuromuscular block in the average patient ($1\times ED_{95}$) in order to perform a 'clinical routine' anaesthesia. Accordingly, many patients developed a maximum T_1 depression of 100% (0% T_1 height). Possibly, using a smaller dose would have resulted in more pronounced differences between groups, as onset time and maximum block are better assessed by administering a subparalysing dose.[21]

The onset time can also be influenced by haemodynamic parameters.[22] However, as the anaesthesia regimen was the same and arterial pressure and heart rate were maintained in a normal range during induction and maintenance of anaesthesia in all groups, it can be assumed that the cardiac index did not differ between the groups. Therefore, an influence of haemodynamic parameters on the onset time seems to be unlikely. Retrospectively, we are aware of the fact that a dose–response study might have been able to present differences in maximal neuromuscular block more clearly than our investigation does. However, our study was the first clinical investigation dealing with this topic; we did not know what results we had to expect. Therefore, we decided to use a design suitable to measure the complete time course including the recovery profile, which would not have been possible with a dose–response curve.

Another question is, if the time course of other blocking agents, especially steroidal drugs would be similarly affected by prednisolone. Most experimental studies available have been performed using the steroidal drug vecuronium, coming to different conclusions, as stated above. Parr and colleagues[23] performed a retrospective clinical review in 50 neurosurgical patients. Patients receiving long-term pretreatment with betamethasone required, on average, 75% more vecuronium. These results support the hypothesis that the influence of corticosteroids observed in the present investigation might not be limited to benzylisoquinolones.

The effects of corticosteroids alone on the time course of the neuromuscular block could be considered as moderate. However, they might reach a higher clinical significance if patients receive several drugs known to interfere with the neuromuscular block (e.g. in neurosurgical patients taking anticonvulsants together with steroids). Chronic intake of anticonvulsants leads to reduced sensitivity to neuromuscular blocking agents.[24 25] The combination of two or more drugs suppressing the effect of the neuromuscular blocking drugs might result in a unexpectedly decreased effect of the neuromuscular blocking drug, potentially leading to intraoperative complications as a result of coughing or movements of the patient.

In conclusion, a long-term medication with prednisolone resulted in a shorter duration of an atracurium-induced neuromuscular block in patients with ulcerative colitis or Crohn's disease. The underlying chronic inflammatory bowel disease itself did not influence the time course of the neuromuscular block.

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