Effect of renal function on neuromuscular block induced by continuous infusion of mivacurium

M. Blobner, S. Jelen-Esselborn, G. Schneider, R. Mann, M. Kling, P. Luppa, H. J. Schneck and E. Kochs

Summary
We have studied the effect of renal function on the pharmacodynamics of mivacurium. Sixty patients were allocated to three groups according to creatinine clearance: group C (control), creatinine clearance > 50 ml min⁻¹; group P (preterminal renal failure), creatinine clearance < 50 ml min⁻¹ > 20 ml min⁻¹; group T (terminal renal failure), creatinine clearance < 20 ml min⁻¹. Neuromuscular transmission (train-of-four) was monitored using electromyography from the hypothenar muscle with stimulation of the ulnar nerve. After an initial bolus, mivacurium was administered continuously to maintain a T1 of 5 (4)% of baseline. The dose of mivacurium necessary to maintain 95% neuromuscular block was similar in patients with normal renal function and patients with different levels of renal impairment. Recovery from neuromuscular block after ceasing mivacurium infusion was significantly prolonged in patients with preterminal renal impairment. There was a close correlation between mivacurium pharmacodynamics and pseudocholinesterase activity, but not creatinine clearance.

Key words
Neuromuscular block, mivacurium. Complications, renal.

Mivacurium-induced neuromuscular block is expected to be independent of renal function, because of rapid hydrolysis by plasma cholinesterases into inactive breakdown products [1]. However, Phillips and Hunter found that a lower dose rate was necessary to maintain 95% neuromuscular block in patients with normal renal function and patients with different levels of renal impairment. Recovery from neuromuscular block after ceasing mivacurium infusion was significantly prolonged in patients with preterminal renal impairment. There was a close correlation between mivacurium pharmacodynamics and pseudocholinesterase activity, but not creatinine clearance. (Br. J. Anaesth. 1995; 74: 452-454)

Methods and results
This prospective, non-randomized study was approved by the Hospital Ethics Committee and 60 male or female patients gave written, informed consent to participate. The patients were aged 18-70 yr, ASA class II-IV, within 20% of their normal body weight (weight (kg) = height (cm) - 100), and were undergoing elective, intermediate surgical procedures. Patients were excluded if they were receiving drugs known to interfere with neuromuscular transmission. All patients had preoperative measurements of serum creatinine concentration, pseudocholinesterase activity (PChE) and dibucaine number. The activity of pseudocholinesterase inhibited by dibucaine (PChE₅₀) is essential for the hydrolysis of mivacurium and is calculated from the definition of the dibucaine number (Dib):

\[
PChE₅₀ = PChE \times \frac{Dib}{100} \text{(ku. litre}^{-1})
\]

Patients were allocated to one of three groups according to their creatinine clearance (CC), calculated from a formula dependent on sex (females: f = 0.85; males: f = 1), age (yr) serum creatinine (S-Crea) and body weight (BW) [3]:

\[
CC = f \times \left(\frac{140 - \text{age}}{8} \times \frac{\text{BW}}{0.8 \times \text{S-Crea}}\right) \text{(ml min}^{-1})
\]

Patients with creatinine clearance > 50 ml min⁻¹ were classified as having normal renal function (group C, controls), patients with creatinine clearance between 21 and 50 ml min⁻¹ had preterminal renal insufficiency (group P) and patients with creatinine clearance < 20 ml min⁻¹ were included in the end-stage renal failure group (group T, terminal).

Anaesthesia was induced with propofol 1.5 mg kg⁻¹ and fentanyl 2 μg kg⁻¹ and maintained with propofol 5-10 mg kg⁻¹ h⁻¹ and fentanyl 0-5 μg kg⁻¹, according to clinical signs of adequate anaesthesia. Ventilation with 65% nitrous oxide in oxygen was adjusted to maintain an end-tidal carbon dioxide concentration of 4-5%. Nasopharyngeal and skin temperatures were prevented from decreasing by more than 1.5 °C by warming blankets and warm i.v. fluids.

Manfred Blobner, MD, Sabine Jelen-Esselborn, MD, PhD, Gerhard Schneider, MD, Ruth Mann, MD, Michael Kling, MD, Peter Luppa, MD, Hans Joachim Schneck, MD, PhD, Eberhard Kochs, MD, PhD, Institut für Anaesthesiologie and Institut für Klinische Chemie und Pathobiochemie der Technischen Universität München, Klinikum rechts der Isar, Ismaninger Straße 22, D-81675 Munich, Germany. Accepted for publication: October 25, 1994. Correspondence to M.B.
Neuromuscular transmission was monitored by electromyography. The ulnar nerve of the immobilized forearm was stimulated by train-of-four stimuli every 20 s and neuromuscular transmission was measured from evoked electromyograms of the hypothenar muscle. The amplitude of the first twitch response of each train compared with control twitch height (T1) and the ratio of the height of the fourth to the first response (T4:T1) were recorded automatically (Relaxograph, Datex). Clinical events and drugs (e.g., start of infusion, change of infusion rate, infusion cessation) were recorded manually.

After induction of anaesthesia, supramaximal stimulus and control twitch height were assessed. Baseline EMG response was stabilized for 5 min at 100 (3)% before mivacurium 0.15 mg kg\(^{-1}\) was given. As soon as the first twitch returned, an infusion of mivacurium 10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) was started and adjusted to maintain the amplitude of T1 at approximately 5% of baseline (1% \(\leq\) T1 \(\leq\) 9%).

The mean mivacurium infusion rate required for each patient was calculated from 15 min to the end of infusion. Spontaneous neuromuscular recovery was assessed using the following times: recovery 25, infusion cessation to T1 = 25%; recovery 75, infusion cessation to T1 = 75%; recovery 90, infusion cessation to T1 = 90%; recovery index (RI), T1 = 25% to T1 = 75%; and recovery T4: T1\(_0\) infusion cessation to T4: T1 = 70%.

In most patients T1 failed to recover completely to baseline amplitude while T4: T1 reached more than 90%. Therefore, recovery of neuromuscular block was calculated relative to the maximal level of T1 at recovery allowing comparison of patients with different end-points of T1. The final T1 recovery level (85 (16)%) was not accepted unless T4: T1 > 90% and T1 had been stable for more than 10 min.

Statistical analysis was performed using the Kruskal–Wallis and chi-square tests. If significant differences were obvious, the Mann–Whitney U test was used. P values less than 0.05 were considered significant. Bonferroni's correction for multiple comparisons was applied if indicated. Spearman rank correlations were used for calculation of the correlation coefficients from all patients data.

After the initial bolus of mivacurium, an infusion was started in 59 patients. One patient in group T (PChE = 2225 u. litre\(^{-1}\)) developed prolonged neuromuscular recovery of the hypothenar muscles for 2 h after the initial bolus, in contrast with the clinical function of the respiratory muscles. Therefore the initial bolus was not followed by an infusion. After operation polyneuropathy was diagnosed, suggesting a discrepancy between the clinical and relaxograph findings. In a second patient, the infusion of mivacurium had to be stopped because of unexpected end of surgery.

There were no significant differences in patient characteristics (age, sex or body weight) or laboratory data (PChE, dibucaine number, serum electrolytes and PChE\(_d\)) between the three groups (table 1). The median mivacurium infusion rate required to maintain approximately 95% neuromuscular block from 15 min to the end of infusion did not differ significantly between groups, although it was slightly lower in patients with end-stage renal failure. However, in both groups of patients with renal insufficiency the ranges were large compared with controls (table 1). When the infusion was terminated spontaneous recovery from similar levels of neuromuscular block (group C: 95 (95/96)%; group P: 96 (95/97)%; group T: 96 (94/97)%) was significantly longer in group P than in group C (table 1). The infusion rates of mivacurium and recovery times of all patients correlated significantly (\(P < 0.001\)) with pseudocholinesterase inhibited by dibucaine but not with serum creatinine concentration or creatinine clearance.

**Comment**

Degradation of mivacurium by plasma cholinesterases implies that duration of action is prolonged if the activity of plasma cholinesterase is reduced. This is confirmed by significant correlations between mivacurium infusion rates and recovery times with PChE\(_d\) indicating involvement of other systemic diseases, for example impaired hepatic function [4]. In contrast with Phillips and Hunter [2], but in agreement with Ryan [5], we found no correlation between lower PChE concentrations and renal impairment. In patients with severe renal dysfunction, who were well adjusted to medical treatment and not substantially restricted in their daily life, PChE, and also mivacurium infusion rates and recovery times were similar to those of healthy controls.

Despite degradation mainly by plasma cholinesterase, prediction of the pharmacodynamics of mivacurium in patients with impaired function is difficult. The distribution volume of the highly water soluble mivacurium corresponds to the extracellular water compartment [6]. Extracellular volume in patients with impaired renal function is variable, poorly regulated and influenced mainly by individual fluid input and dialysis. Hence, the variability in mivacurium infusion rate and spontaneous recovery

**Table 1. Activity of pseudocholinesterase inhibited by dibucaine (PChE\(_d\)), infusion rates (IR) and recovery data (median (range)) of patients in the three groups with different degrees of renal function (group C = control; group P = preterminal renal insufficiency; group T = end-stage renal failure—terminal). * \(P < 0.05\) compared with group C.**

<table>
<thead>
<tr>
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<th>Group C</th>
<th>Group P</th>
<th>Group T</th>
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<tr>
<td>n</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>PChE(_d) (ku. litre(^{-1}))</td>
<td>3.7 (1.2-6.1)</td>
<td>3.2 (0.87-6.0)</td>
<td>3.5 (0.98-5.6)</td>
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<td>IR ((\mu)g kg(^{-1}) min(^{-1}))</td>
<td>5.7 (3.2-10.7)</td>
<td>5.1 (0.7-13.2)</td>
<td>3.8 (0.5-12.4)</td>
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<tr>
<td>Recovery 25 (min)</td>
<td>5.6 (1.7-9.7)</td>
<td>8.0* (4.3-38.0)</td>
<td>7.3* (3.3-20.8)</td>
</tr>
<tr>
<td>Recovery 75 (min)</td>
<td>11.7 (5.5-29.3)</td>
<td>17.5* (9.3-94.0)</td>
<td>18.0* (6.3-69.3)</td>
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<tr>
<td>Recovery 90 (min)</td>
<td>16.0 (6.8-31.3)</td>
<td>23.0* (12.0-121)</td>
<td>23.2* (9.7-93.0)</td>
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<tr>
<td>Recovery index (min)</td>
<td>6.4 (2.8-19.6)</td>
<td>9.0* (4.4-56.0)</td>
<td>10.0* (2.6-48.5)</td>
</tr>
<tr>
<td>Recovery T4:T1(_0) (min)</td>
<td>17.5 (8.8-32.0)</td>
<td>25.2 (13.7-155)</td>
<td>23.8 (10.3-105)</td>
</tr>
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</table>
in patients with impaired renal function might be explained by differences in extracellular volume between these patients.

Of clinical relevance, however, is prolonged neuromuscular block at the end of anaesthesia. The median recovery index of the control group (6.4 min) compared well with the results of other investigators [6]. The recovery indices in the groups with impaired renal function were only slightly longer. More important than the median values were the wide ranges in both groups with impaired renal function (4–56 min for group P, 3–48 min for group T). Consequently, recovery from inadequate surgical relaxation (T1 = 25%) to possible early extubation (T4:T1 = 70%) occurred after more than 30 min in four of 19 patient with preterminal insufficiency and in two of 19 patients with end-stage renal failure.

Our findings suggest that the dose of mivacurium should be reduced in patients with compromised renal function, if there is additional systemic disease, because there was no close correlation between creatinine clearance and mivacurium pharmacodynamics. Thus in patients with impaired renal function, neuromuscular monitoring is useful, even if neuromuscular block is produced with mivacurium. However, the Relaxograph is of little use in patients with polynephropathy, which is not uncommon in renal insufficiency, as exemplified by our patients.

References