Time course of neuromuscular effects of rocuronium during desflurane anesthesia in patients with or without renal failure

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Background: This study aimed to investigate the neuromuscular effects of 0.6 mg/kg rocuronium under desflurane anesthesia in patients with and without renal failure.

Methods: The neuromuscular effects of rocuronium 0.6 mg/kg under desflurane anesthesia were investigated in 20 patients with renal failure undergoing renal transplantation surgery and in 20 patients with normal renal function. Neuromuscular transmission was monitored using acceleromyography with single stimuli at 0.1 Hz. The onset and 25%, 75%, and 95% twitch recovery times, the recovery of the train-of-four ratio to 70% (TOF70), and the recovery index (25−75%) were recorded.

Results: Block onset was similar in the groups. The 25%, 75% and 95% twitch recovery times, the TOF70 time, and the recovery index were found to be prolonged in patients with renal failure compared to those with normal renal function (e.g. TOF70: 123.1 ± 49.1 vs. 68.7 ± 15.5 min) (P < 0.001). A very strong association between the time to TOF70 and the diagnostic duration of renal failure was found (R² = 0.79, P < 0.001).

Conclusions: The duration of action of a bolus dose of 0.6 mg/kg rocuronium under desflurane anesthesia was increased significantly in patients with end-stage renal failure compared to that of healthy controls and was prolonged according to the duration of renal failure. (Korean J Anesthesiol 2009; 57: 566~71)

Key Words: Chronic renal failure, Desflurane, Rocuronium.

INTRODUCTION

Rocuronium bromide (rocuronium), a monoquaternary amino-steroid with a short onset and an intermediate duration of action, is currently one of the most commonly used neuromuscular blocking agents [1]. Although hepatic uptake and biliary excretion have been suggested to be the main mechanisms of rocuronium metabolism, a previous study has shown that 33% of rocuronium was excreted unchanged in the urine within 24 h with metabolites absent both in plasma and urine [2]. Clearance of rocuronium was reduced by 39% and the duration of the neuromuscular block due to rocuronium 0.6 mg/kg was shown to be prolonged during propofol-based anesthesia in patients with end-stage renal failure compared to that of healthy control patients [3]. Desflurane anesthesia significantly prolonged the duration of action of rocuronium, compared to sevoflurane or propofol anesthesia [4]. Desflurane did not lead to a deterioration of creatinine clearance in patients with preexisting renal impairment [5]. Previous studies of rocuronium in patients with renal failure were performed with isoflurane [6-8] or propofol [3,9] as the main anesthetic agent. Thus, the aim of this study was to compare the pharmacodynamics of a bolus dose of rocuronium under desflurane anesthesia in patients with and without renal failure.

MATERIALS AND METHODS

After obtaining Hospital Ethics Committee approval and
written informed consent, 20 patients with chronic renal insufficiency (American Society of Anesthesiologists physical status classification class II or III) were recruited into the study for elective renal transplantation (n = 18) and cadaver renal transplantation (n = 2) with general anesthesia. A control group consisted of 20 healthy patients with normal renal function (ASA physical status classification class I or II) who were scheduled for elective minor surgery after obtaining written informed consent. Exclusion criteria included pregnancy, hepatic or neuromuscular disease, allergy to any anesthetic agents, and obesity (weight > 130% of ideal body weight). All of the renal failure patients included in the study had a creatinine clearance < 10 ml/min and underwent hemodialysis the day before surgery. Medication for essential therapy of the renal failure patients was continued (furosemide, insulin, prednisolone, etc).

Patients did not receive preanesthetic medication. Anesthesia was induced with 0.2 μg/kg/min of remifentanil injected i.v. over 120 sec, followed by sodium thiopental 3 – 5 mg/kg, administered with 10% desflurane after the loss of consciousness, and maintained with desflurane (1.25 MAC of end-tidal concentration adjusted age) and remifentanil at a dose of 0.05 μg/kg/min with 50% nitrous oxide in oxygen [10]. A 10 min period of volatile anesthetic administration was necessary before a constant 1.25 MAC end-tidal concentration was achieved for desflurane. The ventilation pattern was adjusted to maintain the end-tidal carbon dioxide tension within the range of 35 to 40 mmHg. We monitored the ECGs, pulse oxимetries, capnographies and noninvasive blood pressures (Infinity Delta SC 8000, Draeger Medical Systems, Danvers, USA). Neuromuscular monitoring was started immediately after induction of anesthesia and before administration of the muscle relaxant. The forearm was immobilized in a splint and neuromuscular transmission was monitored by acceleromyography using TOF-Watch® (Organon Ltd, Dublin, Ireland) equipment. Prior to calibration of the TOF-Watch® unit a 5-s 50-Hz supramaximal tetanic stimulus was administered at the ulnar nerve [11]. Immediately thereafter, the acceleration transducer was taped to the volar aspect of the distal phalanx of the thumb, and calibration of twitch height was performed. After initial twitch calibration, the ulnar nerve was stimulated at the wrist every 10 sec using supramaximal single stimuli (square-wave pulses of 0.2 ms) for baseline stabilization. After stabilization of control responses, 0.6 mg/kg rocuronium was administered as an i.v. bolus, and tracheal intubation was performed at the time of maximum twitch depression. All patients with normal renal function were infused with lactated Ringer’s solution as appropriate. Patients with renal insufficiency were infused with 0.9% normal saline as appropriate. Skin temperature over the adductor pollicis was kept above 32°C by wrapping the arm in cotton wool and applying forced air warming. The twitch recordings were evaluated for the following variables: time from the end of injection of rocuronium to maximal twitch suppression (onset); time from the end of injection of the initial dose to recovery of the twitch response to a value of 25%, 75%, and 95% of the control twitch tension; time from 25% to 75% twitch recovery (recovery index); time from end of the injection of the initial dose to a train-of-four (TOF) ratio (T4/T1) of 70% (TOF70). If the connection of the renal vessels was completed before TOF70, the subject was excluded from the study. Thereafter, anesthesia was continued as indicated by individual patient care.

Statistical analysis of the data from the study was performed with the SPSS (SPSS for Windows Release 14.0) statistical package. Student’s t-test was used to compare the pharmacodynamic variables onset time, time to a twitch recovery of 25%, 75%, and 95%, recovery index and TOF70, and the biochemical characteristics between the two groups. The analysis between time to TOF70 and variables in the renal failure group consisted of the examination of the coefficient of determination (R²) in evaluation of the linear regression, where R² was used as a measure of fit of the regression surface. A partial F-test was performed to evaluate the relevance of adding a cofactor to the regression. P < 0.05 was considered statistically significant. Values are reported as the mean ± SD (range).

RESULTS

There were no important differences in sex distribution, age, weight and height of the two groups (Table 1). Patients in the

<table>
<thead>
<tr>
<th>Variables</th>
<th>Renal failure group (n = 20)</th>
<th>Normal renal group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>11/9</td>
<td>10/10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.1 ± 10.3</td>
<td>44.6 ± 10.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.3 ± 9.8</td>
<td>63.7 ± 11.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.8 ± 9.3</td>
<td>164.7 ± 8.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number. There was no difference between groups.
Table 2. Biochemical Characteristics and Diagnostic Duration of Renal Failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Renal failure group (n = 20)</th>
<th>Normal renal group (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>136.6 ± 3.7 (129.9 – 143.1)</td>
<td>138.1 ± 4.6 (132.2 – 145.8)</td>
<td>0.263</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>4.5 ± 0.8 (3.4 – 6.3)</td>
<td>4.2 ± 0.6 (3.2 – 5.1)</td>
<td>0.188</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>1.116 ± 0.113 (0.890 – 1.410)</td>
<td>1.172 ± 0.102 (1.007 – 1.361)</td>
<td>0.108</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>56.4 ± 15.8 (31.4 – 101.3)</td>
<td>9.4 ± 1.8 (5.3 – 13.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatine (mg/dl)</td>
<td>9.3 ± 2.9 (4.3 – 15.4)</td>
<td>0.7 ± 0.1 (0.5 – 0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.2 ± 4.9 (23.1 – 39.1)</td>
<td>38.9 ± 5.1 (31.2 – 45.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.3 ± 0.5 (3.3 – 5.1)</td>
<td>4.5 ± 0.6 (3.5 – 5.8)</td>
<td>0.259</td>
</tr>
<tr>
<td>Diagnostic duration (years)</td>
<td>6.8 ± 4.2 (1 – 16)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD (range).

Table 3. Neuromuscular Blocking Properties after Rocuronium (0.6 mg/kg)

<table>
<thead>
<tr>
<th>Duration (min)</th>
<th>Renal failure group (n = 20)</th>
<th>Normal renal group (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time</td>
<td>4.1 ± 2.3</td>
<td>3.2 ± 1.2</td>
<td>0.129</td>
</tr>
<tr>
<td>Time to 25% TOF</td>
<td>62.1 ± 22.3</td>
<td>41.6 ± 11.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to TOF70</td>
<td>123.1 ± 49.1</td>
<td>68.7 ± 15.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recovery index</td>
<td>32.8 ± 15.3</td>
<td>14.7 ± 5.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD. TOF70: recovery to a TOF ratio of 70%.

renal failure group frequently had quite severe pathology related to their renal disease including hypertension, anemia, diabetes mellitus, cardiomegaly, and pulmonary congestion. These complications were not present in the control group. Urea and creatinine plasma concentrations were significantly higher in patients with renal failure compared to those with normal renal function (P < 0.001), whereas plasma electrolyte values were similar in both groups (Table 2). Two patients in the renal failure group had potassium levels above 6 mEq/L (range 3.4 – 6.3 mEq/L), while all patients in the normal renal function groups had potassium levels within normal limits. Hematocrit values were significantly lower in the patients with renal failure compared to those with normal renal function (P < 0.001) (Table 2).

The neuromuscular block characteristics after 0.6 mg/kg of rocuronium are given in Table 3. The spontaneous recovery of TOF70 was not achieved in two patients with normal renal function and more surgical relaxation was needed before such recovery. Three patients with renal failure did not sponta-}

neously reach a TOF70 until complete connection of the renal vessels. The onset time was no different between the groups. The times to recovery of T1 to 25%, 75% and 95% and of the TOF70, and the recovery index were found to be significantly prolonged in the renal failure patients compared to those with normal renal function (P < 0.001). The linear dependence of the time to TOF70 on diagnostic duration illustrated a very strong association (R² = 0.79, P < 0.001) (Fig. 1). A significant degree of association was found between the time to TOF70 and BUN levels (R² = 0.23, P = 0.038) (Fig. 2). However, a poor degree of association was found between the time to TOF70 and creatinine levels (R² = 0.01, P = 0.649) (Fig. 3).

Fig. 1. The linear dependence of the time to TOF70 on the diagnostic duration during neuromuscular blockade caused by rocuronium (0.6 mg/kg) in the patients with renal failure is illustrated. Adjusted: R² = 0.79, P < 0.001. The individual data points and exponential fitted curve are shown.

Fig. 2. The linear dependence of the time to TOF70 on BUN levels is illustrated. Adjusted: R² = 0.23, P = 0.038. The individual data points and exponential fitted curve are shown.

Fig. 3. The linear dependence of the time to TOF70 on creatinine levels is illustrated. Adjusted: R² = 0.01, P = 0.649. The individual data points and exponential fitted curve are shown.
DISCUSSION

We investigated the duration of action of 0.6 mg/kg rocuronium increased to 179% during desflurane anesthesia in patients with end-stage renal failure compared with that of healthy controls. We reported a very strong association between the time to TOF70 and the duration of renal failure.

Kumar et al. [12] reported the respective times after 0.6 mg/kg rocuronium during desflurane anesthesia to recovery of the first response in the TOF stimulation to 25%, 90%, TOF70 and recovery index were 36 ± 8.3 min, 54 ± 15.4 min, 66 ± 13.4 min and 14 ± 5.3 min, respectively, which corresponded with our results. Wulf and colleagues [13] found the intensity of the neuromuscular block of rocuronium to be enhanced by sevoflurane and desflurane compared with that of total intravenous anesthesia (propofol/fentanyl), whereas this therapy did not result in significant effects on the duration of or recovery from the block. Bock and colleagues [14] found that patients receiving sevoflurane, isoflurane or desflurane showed comparable slopes of the dose-response curves of rocuronium, and the curves were shifted to the left compared with those obtained during propofol anesthesia. The same study did not show significant differences regarding the time to spontaneous recovery from a TOF ratio of 0.25 to 0.7 among groups. The discrepancy in the results between previous studies and our study is probably due to differences in the time of administration of volatile anesthetics and the dose of rocuronium used. In another study, desflurane anesthesia significantly prolonged the duration of action of rocuronium at 0.9 mg/kg single bolus dose, compared to sevoflurane or propofol anesthesia maintenance regimens [4], which was similar to the results of our study in healthy patients. The establishment of steady-state conditions requires a period of 30−45 min of volatile anesthetic administration before the administration of the neuromuscular blocking agent [15], and hence this sequence bears little relevance to routine clinical practice. In order to simulate clinical conditions, we started the administration of volatile anesthetic with 10% desflurane immediately after the loss of consciousness, ventilated for 10 min, and then administered rocuronium after an end-tidal concentration of 1.25 MAC was achieved.

Robertson and colleagues [3] demonstrated that clinical duration and the time to TOF70 during propofol anesthesia were prolonged in the renal failure group compared to those of the control; 49 vs. 32 min and 88 vs. 55 min, respectively, and showed similar onset times. Kocabas and colleagues [9] also demonstrated that the neuromuscular effects of 0.6 mg/kg rocuronium under propofol anesthesia were markedly prolonged in young and elderly patients with renal failure compared to patients with normal renal function (e.g., T1 25%: 58.4 ± 20.2 and 80.1 ± 23.7 min vs. 32.8 ± 5.6 and 46.3 ± 9.0 min, respectively) with no difference in the onset times of rocuronium. In the present study, the duration of rocuronium neuromuscular block was significantly prolonged and recovery
indices were achieved at a longer time in the patients with renal insufficiency compared to patients with normal renal function (e.g., TOF70: 123.1 ± 49.1 vs. 68.7 ± 15.5 min). Onset times of rocuronium were similar for the groups. Several factors have been suggested to explain the prolonged duration of action of rocuronium in patients with end-stage renal failure including the reduced clearance rate by 39% in renal failure patients compared to control, with an 84% increase in the mean residence time of rocuronium [3]. Cooper and colleagues [7] demonstrated that there were significant differences between patients with and without renal failure in the rates of clearance (2.5 ± 1.1 ml/kg/min and 3.7 ± 1.4 ml/kg/min, respectively) and in mean residence times (97.1 ± 48.7 min and 58.3 ± 9.6 min, respectively). The higher concentration of rocuronium present in the renal failure group at a TOF70 has also been reported. This may be due to an altered sensitivity of the receptors in renal failure patients. Szenohradszky and colleagues [8] demonstrated that the volume of distribution at steady state was greater in renal transplant patients (264 ± 19 ml/kg) than in control patients (207 ± 14 ml/kg). This resulted in a longer elimination half life in renal transplant patients (97.2 ± 17.3 min) compared to that of the controls (70.9 ± 4.7 min). Another possibility is that nonspecific rocuronium sites are saturated with endogenous compounds thus causing an increase in the plasma concentration and limiting redistribution. This effect could be caused by the high urea, concurrent medication, electrolyte imbalances or the original disease process (e.g., diabetes, hypertension, etc).

An important finding in the present study was that the linear dependence of the time to TOF70 on diagnostic duration illustrated a very strong association (R² = 0.79, P < 0.001). However, a lesser degree of association was found between the time to TOF70 and the BUN (R² = 0.23, P = 0.038) or creatinine (R² = 0.01, P = 0.649) levels. Kim [16] demonstrated that the clinical duration of vecuronium had a significant correlation with the diagnostic duration of chronic renal failure, although a minor relationship with other factors such as age, weight, height, albumin, electrolytes, BUN, creatinine, and hematocrit was observed. Murphey and colleagues [17] demonstrated that osteoporosis and osteomalacia caused osteopenia and were not infrequent associations of chronic renal failure. The prevalence of calcifications increased with the duration of hemodialysis. The other major group of musculoskeletal abnormalities attributable to chronic renal failure included aluminum deposition, amyloid deposition and destructive spondyloarthropy, tendon rupture, crystal deposition, infection, and avascular necrosis. These changes were less common than those of renal osteodystrophy and were more frequently seen in patients who have undergone long-term hemodialysis. Perhaps these abnormal changes of the musculoskeletal system following years of dialysis strongly influenced the correlation with the time to TOF70. At all stages of renal insufficiency, the creatinine level was a much more reliable indicator of renal function than was the BUN level because the BUN was far more likely to be affected by dietary and physiologic conditions not related to renal function [18]. We cannot demonstrate the major causes of a better association of BUN than that of creatinine with the time to TOF70. This relationship needs further study.

The renal patients in this study were undergoing renal transplantation. This may have altered the elimination characteristics of rocuronium after complete connection of renal vessels. Three patients with renal failure were excluded because TOF70 was not spontaneously reached and was only reached upon complete connection of the renal vessels.

These results demonstrate that the neuromuscular effects of 0.6 mg/kg rocuronium under desflurane anesthesia are markedly prolonged in patients with renal failure compared to patients with normal renal function, and the effects are enhanced according to the duration of renal failure. Therefore, careful monitoring of neuromuscular transmission should be performed to prevent overdose of neuromuscular blockers in renal failure patients.

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