Rocuronium does not Induce Serum Tryptase Elevation

Kościuczuk U*, Kosel J1, Siemiątkowski A1, Mroczko B2, Groblewska M3

1Department of Anesthesiology and Intensive Care, Medical University of Białystok, Poland
2Department of Neurodegenerative Diseases Diagnostics, Medical University of Białystok, Poland
3Department of Biochemical Diagnostics, Medical University of Białystok, Poland

Submission: February 15, 2017; Published: June 19, 2017

*Corresponding author: Urszula Kościuczuk, Department of Anesthesiology and Intensive Care, University Clinical Hospital, Białystok, Poland, Tel: 48 857 46 8302; Fax: (85) 74 68 632; E-mail: urszula.kosciuczuk@umb.edu.pl

Abstract

Introduction: Rocuronium is a aminosteroid structured, non-depolarizing neuromuscular blocking agents (NMB). Epidemiological data presents that the frequency of hypersensitivity reactions caused by rocuronium have been increased. Determinations of serum tryptase concentrations are interdisciplinary recommended in diagnosis of its adverse reactions. No studies have been performed to explain specific role of rocuronium doses on serum tryptase values. The aim of this study was to investigate the potential effect of rocuronium on serum tryptase concentrations.

Patients and method: The study included 126 women given a general volatile anesthesia: group I - 66 - using the rocuronium and group II - 60 - without neuromuscular relaxants. Information's about perioperative fluid therapy and doses of rocuronium were noticed. The blood samples were collected to perform tryptase concentration analysis: preoperatively – before anesthesia and postoperatively - after recovery from anesthesia.

Results: Median preoperatively serum tryptase concentration in group I was 2.92 and 3.27 mcg/L in group II, respectively. The reduction of serum tryptase value was noticed in both groups and attained the level of 2.60 mcg/L in group I and 2.79 mcg/L in group II after anesthesia, (p<0.05). Analysis did not show a correlation between the serum tryptase levels and the values connected to the administration of rocuronium and perioperative fluid therapy. No significant differences in the tryptase concentration between the groups were identified.

Conclusion: In conclusion, the scheme of volatile anesthesia with rocuronium did not induced any significant changes in tryptase serum levels compared with the volatile method. The study excluded the serum tryptase concentration dependence of rocuronium and crystalloid dilutional effect. The most likely explanation of our results are physiological changes and specific rhythm of fluctuations of tryptase secretion. It seems prudent to confirm the effect of rocuronium on serum tryptase on larger cohort of patients.

Keywords: Tryptase; Mast cell; Rocuronium

Introduction

Perioperative hypersensitivity and anaphylaxis are important issues in anaesthesiology because its occurrence is related to drugs and agents used in general anesthesia [1-4]. The greatest risk of hypersensitivity occurs during anesthesia for female patients and it is connected with the induction phase using skeletal muscle relaxants [5-7]. Aminosteroids including rocuronium cause hypersensitivity much more often than isoquinoline derivatives and depolarizing agent. Due to the fact that no hypersensitivity to inhalational anesthetic agents has been shown only volatile induction and maintenance of anesthesia using an anesthetic sevoflurane does not pose a risk of hypersensitivity [8-9]. Rocuronium - modern, aminosteroid neuromuscular blocker agent has beneficial pharmacodynamic and pharmacokinetic profile. Many authors presented that rocuronium is very good alternative relaxant in Rapid Sequence Induction. Through the presence of sugammadex - specific antagonist of rocuronium, using of this relaxant agent minimize risk of postoperative respiratory failure. Epidemiological data presents that the frequency of hypersensitivity reactions caused by rocuronium have been increased. Due to the multiple advantages reports of triggering allergic or hypersensitivity reactions caused by rocuronium create doubts about the safety of application [10-12].
Determinations of serum tryptase concentrations are interdisciplinary recommended in diagnosis of its adverse reactions. Tryptase is the main serine protease stored and released by activated mast cells – effector cells triggering hypersensitivity and anaphylaxis. Measurements of serum tryptase concentration in normal condition according to the manufacturer’s product information ranges are 1-11.4 mcg/L with the lower detection limit 1mcg/L [13-15]. No studies have been performed to explain specific role of rocuronium doses on serum tryptase values. The aim of this study was to investigate the potential effect of rocuronium on serum tryptase concentrations during general anesthesia.

Experimental

Patients

The study was approved by the Bioethical Committee of the Medical University of Białystok UMB no. R-I-002/286/2009 and was conducted at the Clinic of Anesthesiology and Intensive Therapy of the Medical University of Białystok. The research was conducted on 126 female patients with assessed perioperative risk according to the ASA 1-2 scale, without allergy related diseases, who were divided into two groups according to the method of anesthesia being used. The study was carried out on two groups of patients:

- Group I – 66 patients qualifying for the gynecological operation procedures under general volatile anesthesia with the muscle relaxant - rocuronium.
- Group II – 60 patients qualifying for thyroidectomy under general volatile anesthesia without NMB.

Methods of anesthesia

In the both groups volatile induction and maintenance of anesthesia with inhalational anesthetic sevoflurane (Sevorane, Abbvie) was performed. Analgesia was ensured through the administration of intravenous fractional doses of fentanyl at 2 mcg/kg of body mass (Fentanyl, Polfa S.A.). After the end of the surgical procedure the administration of sevoflurane was stopped and access to fresh gasses was increased. During the induction of anesthesia patients of Group I, after the attainment of adequate level of anesthetic sleep, a skeletal muscle relaxant rocuronium (Esmeron, Organon) was administered dosed at 0.6 mg/kg of body weight and neuromuscular monitoring of muscle function applying four consecutive stimuli or the TOF (Train-Of-Four) method through the TOF-Watch device. Tracheal intubation was performed after reaching a TOF response level of 0. When muscle function returned to TOF (TOF Ratio) of 0.8-0.9. In group II patients no skeletal muscle relaxants were used. After attaining adequate level of anesthetic sleep tracheal intubation was performed.

Serum tryptase concentration analysis

Blood samples were taken during the perioperative period to assess the level of tryptase in blood serum:

- In group I the concentration of tryptase in blood serum was tested in samples taken before the administration of anesthesia, after stopping the infusion of rocuronium and at the end of administration of anesthesia.
- In group II the concentration of tryptase in blood serum was determined from samples taken before and after the administration of anesthesia.

Determination of the concentration of tryptase in blood serum was performed using the immune fluoroenzymatic test UniCap Tryptase manufactured by Pharmacia Diagnostics AB.

Statistical Analysis

Conformity assessment of empirical distribution of studied parameters was performed using the Shapiro-Wilk test. Since most empirical distributions obtained differed significantly from normal distributions a comparison of the data was assessed by non-parametric tests. The differences in the levels of parameters obtained through the period of observation were assessed using the Wilcoxon signed-rank (paired difference) test and to determine the differences in the level of parameters being considered between the groups of patients the Mann-Whitney U test was used. Correlation coefficients were calculated using Spearman’s rank method. Probability values of p < 0.05 were accepted as significant. Group data were expressed as means and standard deviations (SD) or as medians and range when appropriate. Obtained results were subjected to statistical analysis using the STATISTICA12.0 (Stat Soft Inc., Tulsa, OK, United States) software.

Results

Patients of both groups did not differ when considering their age and anthropometric characteristics (Table 1). The study ascertained that the concentration of serum tryptase in both groups of patients became significantly reduced after anesthesia (Figure 1 & 2). The median value of serum tryptase concentrations in group I was 2.92 mcg/L preoperatively and fell to the level of 2.79 mcg/L (p<0.05) after anesthesia. In group II the concentration of tryptase in blood serum was at 3.27 mcg/L and attained the level of 2.60 mcg/L after anesthesia. The reduction concentrations in group I was 2.92 mcg/L preoperatively and fell to the level of 2.79 mcg/L (p<0.05) after anesthesia. In group II the concentration of tryptase in blood serum was at 3.27 mcg/L and attained the level of 2.60 mcg/L after anesthesia.

How to cite this article: Kościuczuk U, Kosel J, Siemiątkowski A, Mroczko B, Groblewska M. Rocuronium does not Induce Serum Tryptase Elevation. J Anest & Inten Care Med. 2017; 3(2) : 555609. DOI:10.19080/JAICM.2017.03.555609
Table 1: Clinical characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Group I n=66</th>
<th>Group II n=60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>46.9 ± 8.7</td>
<td>50.7 ± 15.1</td>
<td>0.207</td>
</tr>
<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>74.9 ± 13.5</td>
<td>77.9 ± 14.7</td>
<td>0.262</td>
</tr>
<tr>
<td>Height (cm) (mean ± D)</td>
<td>168.7 ± 7.5</td>
<td>165.8 ± 9.7</td>
<td>0.079</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>26.83 ± 4.18</td>
<td>26.42 ± 3.12</td>
<td>0.957</td>
</tr>
<tr>
<td>BSA Mosteller’s formula (mean ± SD)</td>
<td>1.87 ± 0.19</td>
<td>1.88 ± 0.18</td>
<td>0.632</td>
</tr>
<tr>
<td>BSA DuBois’a formula (mean ± SD)</td>
<td>1.85 ± 0.17</td>
<td>1.85 ± 0.15</td>
<td>0.895</td>
</tr>
<tr>
<td>Basophiles (%) (mean ± SD)</td>
<td>0.75 ± 1.73</td>
<td>0.48 ± 0.58</td>
<td>0.790</td>
</tr>
<tr>
<td>IgE Total (kl/L) (mean ± SD)</td>
<td>113.71 ± 165.18</td>
<td>196.88 ± 206.23</td>
<td>0.560</td>
</tr>
</tbody>
</table>

Figure 1: Histograms of serum tryptase concentration – mcg/L in group I. A- before anesthesia, B- stop rocuronium infusion, C- after anesthesia. Cases with undetectable tryptase level were assigned an arbitrary of 1 mcg/L.

Figure 2: Histograms of serum tryptase concentration – mcg/L in group II. A- before anesthesia, C- after anesthesia. Cases with undetectable tryptase level were assigned an arbitrary of 1 mcg/L.

In two patients in group II postoperative serum tryptase concentrations were higher than 11.4 mcg/L. In this cases preoperative tryptase values were 20.40 and 19.10 mcg/L and decreased by 4.10 and 2.30 respectively. No significant differences in the concentration of tryptase in serum between the two groups of patients at various levels of anesthesia have been identified through the analysis (Figure 3). We did not show a correlation between the serum concentration and the values connected to the administration of rocuronium and parameters connected with fluid therapy. The concentration of tryptase both at the time of stopping the infusion of rocuronium as well as at the moment of ending anesthesia did not demonstrate a correlation with the administered intubation dose, the dose administered as an infusion or the total dose of that relaxant (Table 2 & 3).
Figure 3: Serum tryptase concentration according to group strata. Horizontal lines present median values, boxes present the range 25th-75th percentile, whiskers present the minimum and maximum range. Arrows (top of the Figure) reflect significant differences with p value <0.05.

Table 2: Correlation of serum tryptase concentration and doses of rocuronium. Correlation coefficients calculated using Spearman’s rank method.

<table>
<thead>
<tr>
<th>Median (Min/Max)</th>
<th>Serum Tryptase Concentration</th>
<th>After Anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stop Rocuronium Infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>intubation dose (mg)</td>
<td>55 (40-70)</td>
<td>0.13</td>
</tr>
<tr>
<td>Infusion time (min)</td>
<td>75 (25-170)</td>
<td>0.12</td>
</tr>
<tr>
<td>Infusion dose (mg)</td>
<td>40 (5-95)</td>
<td>0.1</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>90 (60-155)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 3: Correlation of serum tryptase concentration and total perioperative fluid therapy. Correlation coefficients calculated using Spearman’s rank method.

<table>
<thead>
<tr>
<th>Median (Min/Max)</th>
<th>Serum Tryptase Concentration after Anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Total volume of perioperative fluid</td>
<td></td>
</tr>
<tr>
<td>ml</td>
<td>1200 (750-2500)</td>
</tr>
<tr>
<td>ml/kg</td>
<td>16.56 (8.33-32.46)</td>
</tr>
<tr>
<td>ml/kg/min</td>
<td>0.15 (0.06-0.36)</td>
</tr>
</tbody>
</table>

Discussion
Perioperative hypersensitivity and anaphylaxis reactions are increasing and important subject in anesthesiology. Most reports come from West Europe, Scandinavia, New Zealand and Australia and in this countries incidence was estimated between 1:10 000 – 1:20 000, with mortality rate ranging 3.5-4.7%. Many authors have demonstrated that rocuronium is the neuromuscular blocking agent which causes anaphylaxis or hypersensitivity reactions the most often during general anesthesia. Hypnotic intravenous medicaments, opioids, antibiotics, latex, radiocontrast agents may also induce similar symptoms [2,3,4,7]. Only the volatile method of anesthesia using sevoflurane is not connected with any risk of inducing hypersensitivity reactions or anaphylaxis [1,6]. Many authors have described a female predominance, especially in adverse allergic reactions to muscle relaxants with the female: male ratio 8:1 to 3:1 [3,5-7].

Diagnosis of hypersensitivity reaction connected with neuromuscular blocking agents is complicated. Cross reactivity between myorelaxants groups are very common. Chemical and food allergies exhibit cross reactivity with other chemical groups of medicaments [16,17]. Confirmation of its adverse
reactions should be based on measurements of serum tryptase concentrations and the identification of allergens using skin tests [6,18]. Determination of the serum tryptase value is a very important way of diagnosis and is recommended by international multidisciplinary committees. Due to enzyme stability under different external environmental condition, tryptase determination is a reliable and effective method of confirming the occurrence of anaphylaxis [1-2].

The aim of this study was to investigate the potential effect of rocuronium on serum tryptase concentrations. To minimize the possible confounding from gender factor and make the study more helpful in clinical aspects the study group consisted of women undergoing a gynaecological operation under general anesthesia with rocuronium and the control group - women undergoing a thyroidectomy under general anesthesia without using any neuromuscular blocking agents. The median value of serum tryptase concentrations were in group I 2.92 mcg/L and in group II 3.27 mcg/L, respectively. Comparing preoperative and postoperative serum tryptase values a significant decrease of 0.23 in group I and 0.61 in group II, (p<0.05), was found. In the study we did not observe any symptoms of hypersensitivity reaction during general anesthesia and perioperative period.

Results of the study performed by Laroche et al demonstrated that mean serum tryptase levels in resuscitation during perioperative anaphylaxis was 86.5 mcg/L [19]. The results of our study are similar with Garvey’s observations. After general anesthesia and orthopedic surgery serum tryptase concentration decreased from median value 4.07 to 3.45 mcg/L, giving variation 0.45. Garvey et al considering causes of decreasing serum tryptase concentration during general anesthesia presented a theory of dilutional effect of crystalloid fluids infusion [20]. Many authors have reported the role of intravenous infusion and oral intake on hematological blood parameters [21-23]. However, no such studies have been performed directly for serum tryptase concentrations. In our study no significant differences in fluid therapy between the two groups have been presented. In order to reduce the dilutional effect of crystalloid fluids infusion the blood samples were taken from isolated venopunctured site. Mean volume of intravenous crystalloid fluids administered during anesthesia in the group I was 1274.24 ml, in group II it was 1319.16 ml. Spearman’s analysis did not present any correlation between postoperative serum tryptase concentrations and the parameters of fluid therapy.

The changes of serum tryptase concentration in our study confirm Brown’s at all observations. The authors explained that in absence of anaphylaxis serum tryptase values do not vary more than 2 mcg/L and specific rhythm in the changes of the concentration of serum tryptase fluctuates around 0.26 mcg/L [15]. No studies have been performed to explain specific effects of rocuronium doses for serum tryptase values. In our study group the mean intubation dose of rocuronium reached 56.06 mg, the mean dose given in infusion was 40.37 mg, while the mean total dose was 96.43 mg and the postoperative serum tryptase concentrations did not correlate with parameters of rocuronium doses.

Conclusion

In conclusion, the study ascertained that the serum tryptase concentration in non-allergic female patients became significantly reduced after general anesthesia with rocuronium and the most likely explanation are physiological changes and specific rhythm of fluctuations. Perioperative serum tryptase concentrations did not correlate with parameters of rocuronium doses and parameters of fluid therapy. The scheme of volatile anesthesia with rocuronium did not induce any statistical changes in tryptase serum levels compared with the volatile method. In women without suspected allergic medical history using of rocuronium as neuromuscular blocking agent during volatile general anesthesia is save. The limitation of our study was a relatively small number of patients examined, and it seems prudent to confirm the effect of rocuronium on serum tryptase on larger cohort of patients.

References