

Rocuronium does not Induce Serum Tryptase Elevation



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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 anesthesiology 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 trypsin concentrations are interdisciplinary recommended in diagnosis of its adverse reactions. Trypsin is the main serine protease stored and released by activated mast cells – effector cells triggering hypersensitivity and anaphylaxis. Measurements of serum trypsin 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 trypsin values. The aim of this study was to investigate the potential effect of rocuronium on serum trypsin 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 4 continuous infusion of rocuronium at a speed required achieving TOF 0 was administered. The continuous infusion of rocuronium was stopped at the moment of surgical closing of the peritoneal cavity. After the appearance of respiratory movement and the return of neuromuscular function to the level of TOF 25% 0.5 mg of atropine (Atropinum sulfuricum, Polfa) and 1.5 mg of neostigmine (Polstygmina, Pliva) was administered intravenously. Extubation was performed in hemodynamically

stable patients with preserved, normal spontaneous respiratory function at TOFR (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 trypsin concentration analysis

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

In group I the concentration of trypsin 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 trypsin in blood serum was determined from samples taken before and after the administration of anesthesia.

Determination of the concentration of trypsin in blood serum was performed using the immune fluoroenzymatic test UniCap Trypsin 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 trypsin in both groups of patients became significantly reduced after anesthesia (Figure 1 & 2). The median value of serum trypsin concentrations in group I was 2.92 mcg/L preoperatively and fell to the level of 2.60 mcg/L after anesthesia. The reduction of concentration of trypsin in serum was also noticed in group II and before anesthesia was at 3.27 mcg/L and attained the level of 2.79 mcg/L ($p < 0.05$) after anesthesia. In group I the drop in the concentration of trypsin in blood serum after the finish rocuronium infusion and after the end of administering anesthetics was 10.62 and 10.96% ($p < 0.05$), respectively. In group II the recorded decrease in the concentration of trypsin in blood serum after anesthesia reached 14.68% ($p < 0.05$).

Table 1: Clinical characteristics of patients.

	Group I n=66	Group II n=60	p
Age (years)(mean ± SD)	46,9 ± 8,7	50,7 ± 15,1	0,207
Weight (kg)(mean ± SD)	74,9 ± 13,5	77,9 ± 14,7	0,262
High (cm)(mean± D)	168,7± 7,5	165,8 ± 9,7	0,079
BMI (mean ± SD)	26,83 ± 4,18	26,42 ± 3,12	0,957
BSA Mosteller's formula (mean ± SD)	1,87 ± 0,19	1,88 ± 0,18	0,632
BSADuBois'a formula (mean ± SD)	1,85 ± 0,17	1,85 ± 0,15	0,895
Basofiles (%) (mean ± SD)	0,75± 1,73	0,48±0,58	0,790
IgE Total (kU/L) (mean ± SD)	113,71±165,18	196,88±206,23	0,560

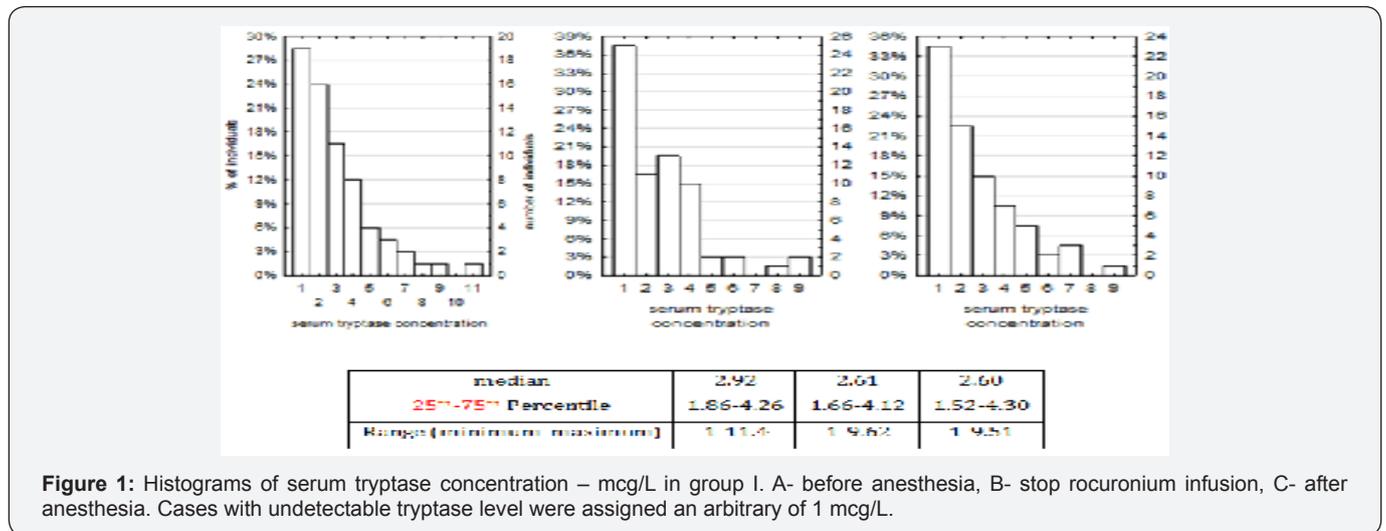


Figure 1: Histograms of serum tryptase concentration – mcg/L in group I. A- before anesthesia, B- stop rocuronium infusion, C- after anesthesia. Cases with undetectable tryptase level were assigned an arbitrary of 1 mcg/L.

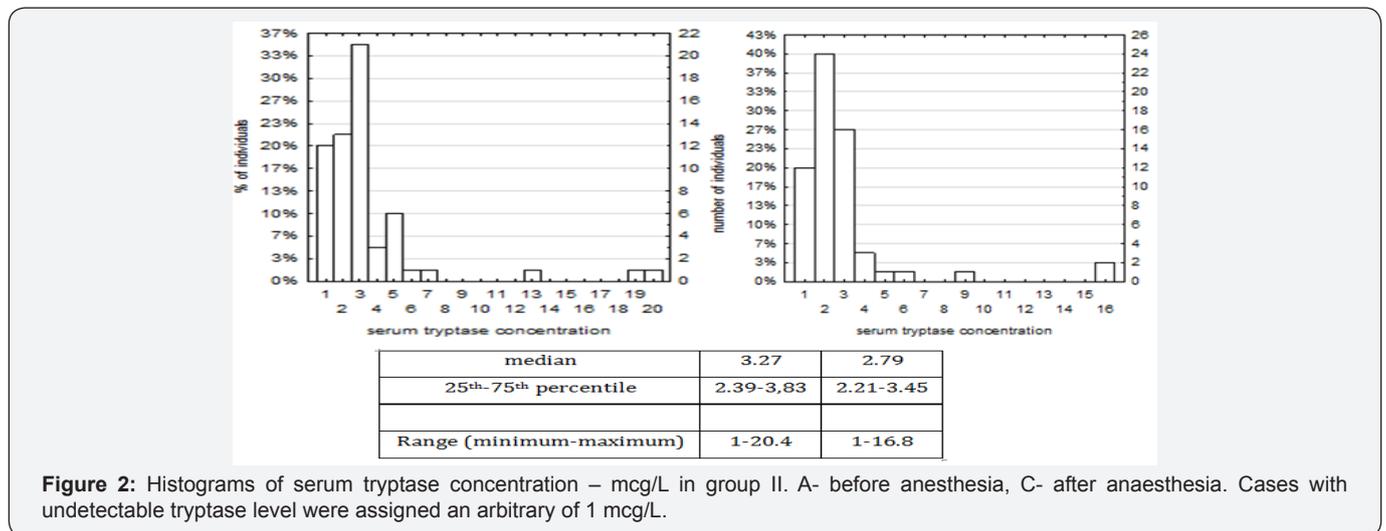


Figure 2: Histograms of serum tryptase concentration – mcg/L in group II. A- before anesthesia, C- after anaesthesia. Cases with undetectable tryptase level were assigned an arbitrary of 1 mcg/L.

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).

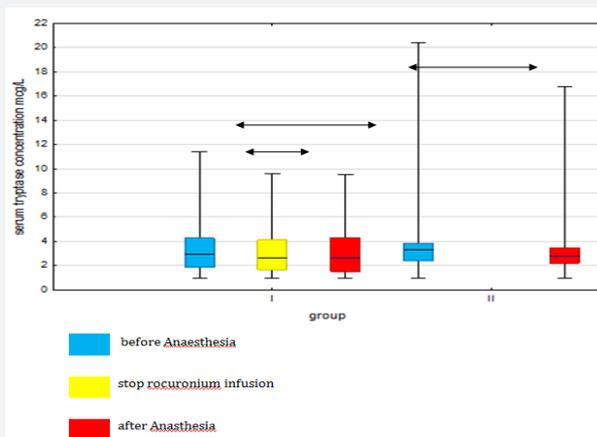


Figure 3: Serum tryptase concentration according to group strata. Horizontal lines present median values, boxes present the range 25th-75th percentile, whiskers present the minimum and maximum range. Arrows (top of the Figure) reflect significant differences with p value <0.05.

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

	Median (Min/Max)	Serum Tryptase Concentration			
		Stop Rocuronium Infusion		After Anaesthesia	
		R	P	R	p
intubation dose (mg)	55 (40-70)	0.13	0.794	0.23	0.828
Infusion time (min)	75 (25-170)	0.12	0.349	0.13	0.296
Infusion dose (mg)	40 (5-95)	0.1	0.394	0.13	0.286
Total dose (mg)	90 (60-155)	0.11	0.398	0.13	0.304

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

	Median (Min/Max)	Serum Tryptase Concentration after Anaesthesia		
		R	p	
Total volume of perioperative fluid	ml	1200 (750-2500)	0.17	0.447
	ml/kg	16.56 (8,33-32.46)	0.23	0.715
	ml/kg/min	0.15 (0.06-0.36)	0.01	0.903

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 gynecological 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.

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