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Effect of General Anesthesia and Orthopedic Surgery on Serum Tryptase

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ABSTRACT

Background: Mast cell tryptase is used clinically in the evaluation of anaphylaxis during anesthesia, because symptoms and signs of anaphylaxis are often masked by the effect of anesthesia. No larger studies have examined whether surgery and anesthesia affect serum tryptase. The aim of this study was to investigate the effect of anesthesia and surgery on serum tryptase in the absence of anaphylaxis.

Methods: The study included 120 patients (median age, 54 yr; range, 19–94 yr) undergoing elective orthopedic surgery in general anesthesia. Exclusion criteria were allergic reactions during this or previous anesthesia, hematologic disease, or high-dose corticosteroid treatment. Blood samples for tryptase analysis (ImmunoCAP®; Phadia, Uppsala, Sweden) were drawn shortly before anesthesia and after anesthesia and surgery.

Results: Median duration of anesthesia was 105 min (range, 44–263 min). Median interval between blood samples was 139 min (range, 39–370 min). Mean tryptase before surgery was 5.01 μg/l, with a mean decrease of 0.55 μg/l ($P < 0.0001$; 95% CI, 0.3–0.8) postoperatively. All patients received intravenous fluid (median value 750 ml; range, 200–2000 ml) perioperatively. There was no significant effect of gender, age, American Society of Anesthesiologist's physical status classification, or self-reported allergy on serum tryptase.

Conclusions: Serum tryptase shows small intraindividual variation in the absence of anaphylaxis. A small decrease was observed postoperatively, likely due to dilution by intravenous fluid. On suspected anaphylaxis during anesthesia, tryptase values, even within the normal reference interval, should, when possible, be compared with the patient's own basal level taken more than 24 h after the reaction.

What We Already Know about This Topic

- Serum tryptase concentrations increase during anaphylaxis and have been used to confirm suspected anaphylaxis during anesthesia
- Whether anesthesia itself alters serum tryptase concentration is unknown

What This Article Tells Us That Is New

- In 120 subjects undergoing elective and uneventful surgery, there was a slight decrease in serum tryptase concentration, likely reflecting dilution from intravenous fluids
- Comparison of serum tryptase concentration within 1–4 hr of the event and at least 24 hr later can help confirm suspected anaphylaxis during anesthesia

TRYPTASE is a serine protease mainly stored in mast cell granules. Under normal conditions, serum tryptase consists of protryptase α and β, which are continuously secreted into the bloodstream, making up the basal level of serum tryptase, and this level is believed to be an indicator of the total number of mast cells in the body.[1] Increased number of mast cells leading to increased basal levels of serum tryptase can be seen in hematologic conditions such as mastocytosis.[2] Mature β tryptase is contained in granules in the mast cell and is released only during activation and degranulation of the mast cell. Mast cell degranulation can be triggered by a variety of stimuli, such as C5a and C3a, neuropeptides, and certain drugs, but most commonly occurs when a specific antigen causes cross-linking of specific IgE molecules bound to the high affinity IgE receptor on the surface of mast cells.[3] An increase in serum tryptase is, therefore, highly suggestive of IgE-mediated mast cell activation, when seen in connection with signs and symptoms of anaphylaxis.[4] Such a marker of anaphylaxis has proven to be

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particularly useful in cases where the clinical diagnosis is uncertain, for example, during anesthesia, where symptoms and signs of anaphylaxis are often masked or mimicked by the effect of anesthetics and patient comorbidity. The use of serum tryptase has, thus, been recommended when investigating patients with suspected anaphylactic reactions during anesthesia,[5,6] and the current recommendations are to take a sample 1–4 h after the reaction and compare with a basal level serum tryptase taken minimum 24 h after the reaction.[7] In the Danish Anaesthesia Allergy Centre, serum tryptase has been used routinely since 1999, when investigating patients with suspected allergic reactions during anesthesia. However, the possible effect of anesthesia and surgery *per se* on serum tryptase has only been partially elucidated in smaller studies. These indicate that there is no increase in serum tryptase during coronary bypass surgery using extracorporeal circulation[8] or during cardiac defibrillation with the administration of suxamethonium.[9] The aim of the current study was, therefore, to investigate the effect of anesthesia and surgery *per se* on serum tryptase concentration and to investigate the characteristics of basal levels of serum tryptase in a population of patients undergoing elective orthopedic surgery.

Materials and Methods

Patients

The study was approved by the Ethical Committee for the Capital Region, Copenhagen, Denmark, and included 120 patients undergoing elective orthopedic surgery in general anesthesia. Data storage was approved by the Data Protection Agency, Copenhagen, Denmark. Eligible patients were identified from operating lists the day before surgery. On the morning of scheduled surgery, before the administration of premedication, patients were included in the study, and the written informed consent was obtained. Inclusion took place on a total of 27 days at Bispebjerg Hospital, Copenhagen, Denmark, and a total of 120 patients were included. Inclusion criteria were as follows: patients aged 18 yr or older and scheduled elective orthopedic surgery in general anesthesia with a minimum expected duration of approximately 1 h. To cover the widest possible age range, it was intended to include 60 patients in the age group of 18–60 yr and 60 patients older than 60 yr, but this proved not to be possible because of the design with consecutive inclusion. Exclusion criteria were as follows: pregnancy, previous allergic reactions during anesthesia, corticosteroid treatment of more than 2.5 mg daily, and known hematologic disease including mastocytosis. Patients developing a suspected allergic reaction during anesthesia would also be excluded.

Twelve patients declined to participate in the study for the following reasons: fear of needles (seven patients), did not wish to participate (three patients), and did not speak Danish (two patients). After inclusion, two patients withdrew consent, and in three cases, surgery was cancelled. In these five cases, subsequent patients were included.

Before anesthesia, the following information was recorded: allergy status (self-reported allergy), type of orthopedic surgery, and American Society of Anesthesiologist's physical status classification. During anesthesia, a record was kept of the length of general anesthesia, all drugs administered, use of regional anesthesia, fluid administration, blood loss, administered blood products, and use of inotropes.

Postoperatively, patients and anesthetic charts were examined for signs of anaphylaxis. None of the 120 patients showed signs of an allergic reaction during or after anesthesia.

Because serum IgE was not measured for inhalant allergens, atopy was defined as self-reported allergy symptoms on contact with at least one inhalant allergen (tree/grass pollens, animal dander, house-dustmite, and ambrosia). Self-reported allergy to other allergens, such as drugs, plaster, nickel, were classified as other known allergen.

Blood Sampling

Preoperative blood samples for tryptase analysis were drawn shortly before anesthesia, in most cases, during insertion of the intravenous cannula. The postoperative blood sample was collected approximately at 1–4 h after anesthesia induction, as mast cell tryptase increase after anaphylaxis is seen in this time interval. Blood samples were collected, according to the standard procedure in our laboratory, as whole blood in plain collection tubes and were transported at room temperature. Samples were sent to the laboratory for analysis the following weekday.

Tryptase analysis was performed at the Laboratory for Allergy, Copenhagen University Hospital, Rigshospitalet, Denmark, using ImmunoCAP® (Phadia, Uppsala, Sweden) measuring total tryptase in serum, that is, all proforms of α tryptase and β tryptase, and mature β-tryptase. According to the manufacturer's product information (ImmunoCAP®, Tryptase in anaphylaxis, 2007), a study of 126 healthy individuals with an age range of 12–61 yr yielded an upper ninety-fifth percentile for basal levels of serum tryptase of 11.4 μg/l, and a median value of 3.8 μg/l with a lower detection limit of 1 μg/l. This forms the basis for the currently recommended normal reference interval.

Statistical Analysis

Analysis of sample size needed (n = 120) was carried out using the Altman nomogram.[10] From 118 measurements of baseline values of mast cell tryptase in the Danish Anaesthesia Allergy Centre patients, the SD was calculated to be 5 μg/l. Because there were no previous studies examining differences in preoperative and postoperative serum tryptase, we had no knowledge of the correlation between preoperative and postoperative values, and thus, the power calculation was based on unpaired analysis (a conservative procedure). The clinically relevant difference was determined to be more than or equal to 3 μg/l, that is, standardized difference 0.6 with power 0.9 and significance level 0.05.

Serum tryptase levels preoperatively and postoperatively were compared using paired Student *t* test. Because tryptase concentrations did not follow a normal distribution, differences in serum tryptase levels in groups of patients older than

Table 1. Characteristics and Median Preoperative Serum Tryptase Values for Elective Orthopedic Surgery Patients (n = 120)

	Patients, n (%)	Serum Tryptase (μg/l), Median (Interquartile Range)	*P* Value
Age group, yr			
< 60	75 (62.5)	4.09 (3.08–5.04)	0.9*
≥ 60	45 (37.5)	4.04 (2.68–5.47)	
Sex			
Female	60 (50.0)	4.32 (2.47–6.03)	1.0*
Male	60 (50.0)	4.00 (3.19–5.11)	
ASA classification†			
I	60 (50.0)	4.02 (2.92–4.89)	0.7‡
II	51 (42.5)	4.09 (2.96–6.41)	
III	9 (7.5)	4.91 (3.88–5.34)	
IV	0	N/A	
Self-reported allergy			
Yes	43 (35.8)	3.85 (2.97–4.91)	0.6*
No	77 (64.2)	4.30 (2.96–5.64)	
Atopy			
Yes	21 (17.5)	3.98 (3.52–4.72)	0.5*
No	99 (82.5)	4.14 (2.73–5.64)	
Other known allergen			
Yes	28 (23.3)	3.87 (2.15–5.38)	0.8*
No	92 (76.7)	4.15 (3.10–5.32)	

* Unpaired *t* test after logarithmic transformation. † American Society of Anesthesiologists (ASA) physical status classification. ‡ Analysis of variance after logarithmic transformation.

and younger than 60 yr, between males and females, and in patients with or without self-reported allergy were compared using unpaired *t* test after logarithmic transformation. Association between tryptase values and American Society of Anesthesiologist's physical status classification was assessed using ANOVA after logarithmic transformation. Linear regression was performed looking for a relation between age and preoperative levels of serum tryptase after logarithmic transformation. *P* values of < 0.05 were considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 120 patients (60 men/60 women; median age 54 yr; range, 19–94 yr) were included. Median preoperative serum tryptase values can be seen in table 1. There was no significant effect of gender, age group, or American Society of Anesthesiologist's physical status classification on serum tryptase. Linear regression showed no correlation between age and preoperative levels of serum tryptase ($r = 0.05$, $P = 0.6$).

A total of 43% of patients reported to have one or more allergies. Atopy was present in 21% of patients, and 28% had self-reported allergy to drugs, mostly penicillin (12 patients) or other allergens, mostly plaster (7 patients). There was no significant effect of overall self-reported allergy status, atopy, or other known allergen on serum tryptase.

Variations in serum tryptase, both whole population and intraindividual variation, can be seen in table 2. Preoperative tryptase samples were used as a measure for the whole population variation with a median value of 4.07 μg/l (range,

Table 2. Variation in Serum Tryptase during Orthopedic Surgery

	Serum Tryptase (μg/l)	
n = 120	Median (Interquartile Range)	Mean (SD)
Whole population variation		
Preoperative sample* (range, 1.0 to 35.8)	4.07 (2.97 to 5.32)	5.01 (4.52)
Postoperative sample* (range, 1.0 to 31.9)	3.45 (2.67 to 4.74)	4.46 (3.80)
Intraindividual variation		
Postoperative–preoperative samples (range, 6.7 to −8.0)	−0.45 (−0.87 to 0.00)	−0.55 (1.39)

Whole population variation and intraindividual variation are shown.

* Paired Student *t* test, $P < 0.0001$ (95% CI 0.30–0.80).

1.00–35.80 μg/l) and an upper ninety-fifth percentile of 13.05 μg/l. Mean value for preoperative samples was 5.01 μg/l, and mean value for postoperative samples was 4.46 μg/l, giving a statistically significant decrease in serum tryptase during surgery and anesthesia, mean decrease 0.55 μg/l ($P < 0.0001$, 95% CI 0.30–0.80).

The SD on the change between preoperative and postoperative value was 1.39 μg/L, giving a reference interval of (−3.33 to 2.23 μg/l), meaning that 95% of patients are expected to have a change in serum tryptase in the interval between a decrease of 3.33 μg/l and an increase of 2.23 μg/l.

Calculating the difference between postoperative and preoperative values after logarithmic transformation, a mean decrease of 9% (95% CI, 6–13%) was found. The reference interval for ratios was (0.59–1.39), meaning that 95% of patients are expected to have a change in serum tryptase in the interval between a 41% decrease and a 39% increase.

Only two patients had an increase in serum tryptase of more than 2.23 μg/l (mean + 2SD) with increases of 2.57 and 6.72 μg/l, respectively. Neither of them showed signs or symptoms of an allergic reaction nor reported any known allergies or atopy.

Preoperative serum tryptase values were more than the manufacturers recommended upper limit of 11.4 μg/l in 7 of 120 (5.8%) of patients (table 3). Four of these patients showed a decrease in tryptase of more than 3.33 μg/l (mean − 2SD). There was no statistically significant difference in the age between patients with serum tryptase more than and less than 11.4 μg/l.

Median duration of anesthesia was 105 min (range, 44–263 min), and median interval between blood samples before and after surgery was 139 min (range, 39–370 min). Because of unexpected surgical delay in four cases, the postoperative sample was taken before surgery was completed. In all cases, at least 2 h elapsed between presample and postsample, and mean difference in tryptase for these four patients was 0.57 μg/l, that is, very close to the overall result. In one case, the presample was taken more than 15 min after induction, and only 39 min elapsed between tests, but as pretest and posttest results were identical (less than 1 μg/l), this was not believed to affect the overall result. All patients were given intravenous fluids (median, 750 ml; range, 200–2000 ml) during surgery.

Table 3. Characteristics for Orthopedic Surgery Patients with Preoperative Serum Tryptase Values More than and Less than 11.4 μg/l* (n = 120)

	Tryptase ≤ 11.4 μg/l	Tryptase > 11.4 μg/l	*P* Value
Patients, n (%)	113 (94.2)	7 (5.8)	
Female, n (%)	55 (92)	5 (8)	
Male, n (%)	58 (97)	2 (3)	
Age (yr), mean ± SD	51.5 ± 17.6	61.6 ± 19.3	0.15†
Median serum tryptase, μg/l	3.98	14.8	

* Manufacturer's recommended upper limit for normal serum tryptase. † Unpaired *t* test for means.

Discussion

The aim of this study was to investigate the potential effect of anesthesia and surgery on serum tryptase. To minimize the possible confounding from type of surgery, we chose to investigate a population of patients undergoing elective orthopedic surgery in general anesthesia. A recent study of intestinal handling during abdominal surgery showed that mast cell activation and tryptase release were induced locally in peritoneal fluid, although this was not accompanied by an increase in serum tryptase.[11]

Comparing preoperative and postoperative samples of serum tryptase in a population of patients undergoing elective orthopedic surgery in general anesthesia, we found a mean decrease of 0.55 μg/l, and the most likely explanation is a dilutional effect of intravenous fluid therapy. Studies examining hemoglobin have found a dilutional effect of crystalloid fluids in healthy volunteers[12] and a small dilutional effect of general anesthesia, in the absence of fluid administration, during laparoscopic surgery.[13] No such studies have been performed for serum tryptase, and our study was not designed to examine the potential dilutional effect of intravenous fluids on serum tryptase. Thus, further studies would have to be undertaken to confirm the mechanism behind the decrease in serum tryptase.

The decrease observed in our study is statistically significant, but it is of minimal clinical importance in daily practice in the absence of suspected anaphylaxis. If intravenous fluids had not been administered, an even smaller change in serum tryptase may have been expected, as reported by Brown *et al.*[14] who found a mean difference in serum tryptase basal levels of 0.26 μg/l, when comparing samples taken from the same individual 14 weeks apart. The authors concluded that in the absence of anaphylaxis, tryptase values do not vary more than 2 μg/l in the same individual. Our study shows that during orthopedic surgery in general anesthesia, in the absence of anaphylaxis, 95% of patients showed a change between preoperative and postoperative values of serum tryptase in the interval between a decrease of 3.33 μg/l and an increase of 2.23 μg/l. Because changes were greater for higher serum tryptase values, calculations giving a percentage change might be more precise, and 95% of patients had a change in serum tryptase in the interval between a 41% decrease and a 39% increase. Thus, serum tryptase shows only small intraindividual variation even in the orthopedic surgical setting. In cases of clinical suspicion of anaphylaxis during anesthesia, current recommendations are that a serum tryptase sample should be taken within 1–4 h of the reaction and a note should be made of the timing of the sample in relation to the suspected allergic reaction. Also, this tryptase concentration should be compared with the patient's own basal level of serum tryptase taken at least 24 h after suspected

anaphylaxis.[7] A preoperative basal level serum tryptase could also be used for comparison, but it is rarely available in clinical practice. Our data show that the variation in the whole population as expressed by SD in preoperative levels of serum tryptase is much greater than the intraindividual variation SD 4.52 *versus* 1.39 μg/l, respectively (table 2).

Because of this small intraindividual variation in serum tryptase level, clinically relevant increases within the normal reference range have been reported previously, and this should be kept in mind when interpreting tryptase values.[15,16] Also, in the setting of anaphylaxis, several liters of fluid may be administered, and the possible dilutional effect could potentially mask a discrete, but clinically significant increase in serum tryptase.

Our data show slightly higher tryptase concentrations compared with data in the manufacturers product information (ImmunoCAP® Tryptase in anaphylaxis, 2007), partly because a population of elective orthopedic surgery patients is not directly comparable with a population of healthy individuals. However, the age range of 19–94 yr (median 54 yr) in our population is broader than the age range of 12–61 yr (no median quoted) in the manufacturer's healthy individuals.

Preliminary results from the Danish Anaesthesia Allergy Centre previously suggested that in patients referred for investigation of allergic reactions during anesthesia, an increase in basal levels of serum tryptase might be seen with an increase in age.[17] In the literature, only two studies of patients with venom allergy has found an association between increasing age and basal levels of serum tryptase#.[18] No literature could be found on a possible age effect on basal levels of serum tryptase in patients investigated for drug allergy or anesthesia allergy.

In this study, samples taken preoperatively, before any intervention on the patient, are used as a measure for basal levels of serum tryptase in this patient population. Looking at these samples, there was no significant effect of gender, age group (less than or more than 60 yr), or American Society of Anesthesiologist's group on mean serum tryptase level. In addition, linear regression showed no correlation between age and preoperative levels of serum tryptase. A possible relation between age and serum tryptase could, thus, not be found in this population of elective orthopedic surgery patients, and studies of patients with suspected allergic reactions during anesthesia would be needed to further elucidate this.

We found no statistically significant association between self-reported allergy or atopy and preoperative levels of serum tryptase. Previous studies have shown no association between basal levels of serum tryptase and atopy.[15] In our study, only two patients showed an increase in serum tryptase level more than 2.23 μg/l (mean + 2SD), and neither reported any known allergy or atopy. The increase in serum tryptase level could, therefore, be either an expression of the extremes of the normal variation in the test or a sign of some other mechanism of mast cell degranulation. In clinical practice, this phenomenon would most likely go unnoticed, as mast cell tryptase would only be measured in the context of a suspected allergic reaction during anesthesia. It is important, however, to be aware that increases in tryptase level can be seen in the absence of allergic symptoms and signs.

A preoperative level of serum tryptase more than the recommended reference was found in 5.8% of patients in the absence of signs or symptoms of anaphylaxis or mastocytosis (table 3). The relevance of this finding is uncertain. In venom allergic patients with previous severe reactions, studies have indicated that an increased basal level of serum tryptase could be an early sign of mast cell disorder,[19,20] but no such studies have been carried out in patients without signs or symptoms of allergic disease or in patients investigated for drug allergy or anesthesia allergy. Further studies of these groups of patients will be needed to investigate whether findings in venom allergic patients can be extrapolated to other groups of patients.

In conclusion, no increase in serum tryptase concentration was observed in connection with orthopedic surgery in general anesthesia. On the contrary, there was a small, but statistically significant decrease of 0.55 μg/l, most likely due to the dilutional effect of intravenous fluid administration.

In the absence of anaphylaxis, serum tryptase shows only small intraindividual variation, and in the setting of anesthesia and orthopedic surgery, 95% of patients showed a change between preoperative and postoperative values of serum tryptase in the interval between a decrease of 3.33 μg/l and an increase of 2.23 μg/l. Because the recommended upper limit of normal for serum tryptase is 11.4 μg/l, it could be speculated that during suspected anaphylaxis, clinically relevant increases could occur within the normal limits, but this would have to be further studied in a population of patients with suspected allergic reactions during anesthesia and surgery. Until such data are available, it would seem prudent to continue to follow the current recommendations to compare a serum tryptase level taken 1–4 h after a suspected allergic reaction, with the patients' own basal level serum tryptase, in a sample taken minimum 24 h after the reaction.[7]

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