



# Tryptase, a clinical marker to help understand severe reactions<sup>1-9</sup>

Severe reactions to drugs during surgery

# Was it a drug induced anaphylaxis?

Finding the cause of a severe reaction which occurs during surgery can be difficult as many drugs and other agents are administered over a short time period and the symptoms are similar for several kinds of adverse reactions during surgery under general anesthesia.<sup>1-9</sup>



# How can a tryptase test help?

Example: A patient suffering a severe reaction during general anesthesia surgery

## Tryptase helps to explain the reaction and confirm if a mast cell activation occurred

Adverse reactions during surgery are rare, however, when they occur it is important to identify the mechanism and underlying cause. Is it a mast cell mediated reaction or not? Follow up investigations will differ.<sup>3-9</sup>

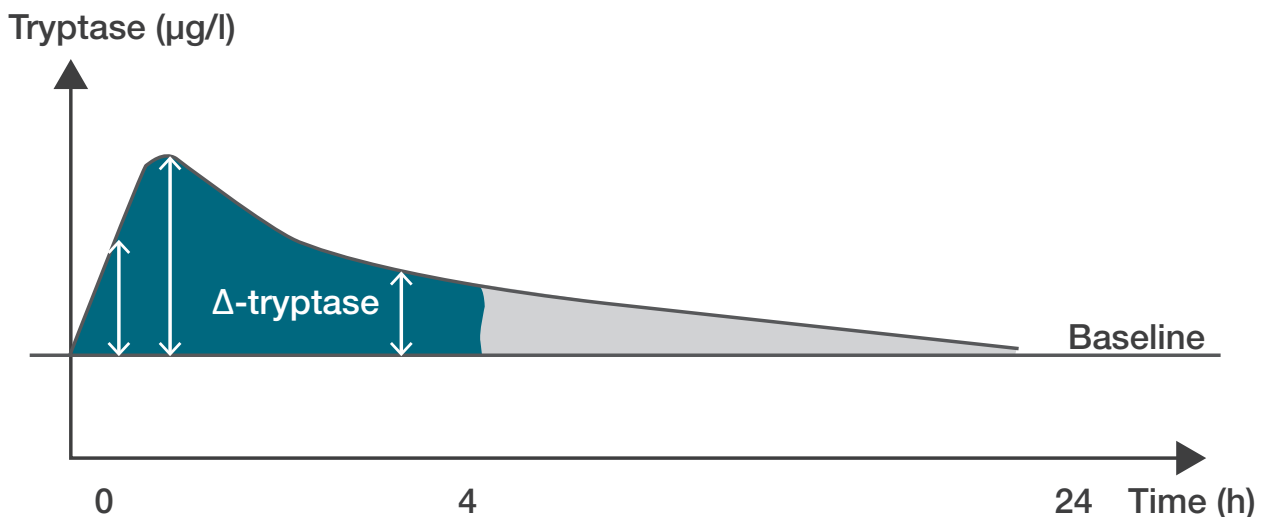
Tryptase results indicate if there was a mast cell activation.<sup>1-9</sup>

Measurements of transiently elevated tryptase level directly after the reaction can help to identify if the reaction was due to mast cell activation.<sup>2-9</sup> If positive, further allergy investigations e.g., specific IgE tests should be performed to find the likely trigger of the reaction.<sup>8,9</sup>

- A transient increase in tryptase concentration shortly (within 15 minutes to 3 hours) after a severe reaction e.g., anaphylaxis, is a marker of mast cell activation.<sup>1,2</sup>
- The tryptase level normally returns to baseline at approx. 24–48 hours after complete resolution of all clinical symptoms.<sup>1,10</sup>
- The baseline tryptase level in each individual is normally very stable over time.<sup>1,2</sup>

The difference between the peak level minus the baseline tryptase level is expressed in this document as delta-tryptase ( $\Delta$ -tryptase).

Below a schematic image in principle describing the course of events.



Confirmation of mast cell activation if the increase in tryptase ( $\Delta$ -tryptase) is at least 20 % above baseline plus 2  $\mu\text{g/l}$ .<sup>1</sup>

**Confirmed mast cell activation:<sup>1</sup>  $\Delta$ -tryptase is  $\geq 20\%$  of the individual's own baseline tryptase + 2  $\mu\text{g/l}$ .**

# Tryptase – A risk marker for future severe reactions

Multiple drugs and other agents used during surgery and anesthesia have the potential to cause an anaphylactic reaction.

- In most cases, a large number of drugs have been administered to the patient, and it could be difficult to pinpoint the cause at the actual time of the reaction.
- 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.<sup>5,11</sup>

For an acute severe reaction life-saving measures will be the same irrespective of underlying cause. However, a follow-up investigation is necessary in order to avoid a potentially life-threatening re-exposure of the patient to the offending substance.<sup>5-9</sup>

## Guiding further investigations

Follow up investigations are necessary:

- When mast cell activation is confirmed by tryptase measurements during and after the acute reaction
- In patients with a probable severe allergic reaction during surgery

Investigations should include measurements of base line tryptase and allergy investigations including relevant specific IgE antibody tests.<sup>5-9</sup> This together with a thorough case history may help identify the underlying cause of the reaction. There is a consensus among associations of allergy specialists that Systemic Mastocytosis is a risk factor for Anaphylaxis and that tryptase determination and examination for signs of mast cell disorders are recommended.<sup>8,9</sup>

The importance of measuring the transient increase of tryptase during the perioperative phase is well established.<sup>3-5,7,11</sup>



## When can you expect transiently increased tryptase levels?

Transient increases of tryptase are most commonly measurable in the blood after severe reactions, that involve respiratory and cardiovascular symptoms. However, also in less severe reactions, transient increases of tryptase may be measured in the blood.

Changes in tryptase levels can also be measured locally after allergen provocations, e.g., in nasal secretions or saliva, thus providing objective challenge measures.<sup>12,13</sup>

Both the occurrence and the magnitude of increased tryptase are more pronounced after IgE mediated reactions than after non-immunological reactions. Increased tryptase is also more commonly seen after parenteral than after oral or inhalant administration of the offending substance.<sup>2,3,8,9,12,14</sup>

### **Agents known to cause IgE mediated mastcell degranulation<sup>3-9,15</sup>**

- Chlorhexidine and other disinfectants
- Neuromuscular blocking relaxants – NMBA, e.g. succinylcholine (suxamethonium)
- Natural Rubber Latex
- Penicillin and other antibiotics
- Hypnotics, e.g., thiopental
- Iodinated radiocontrast dyes
- Opioids, e.g., morphine or structural similarities

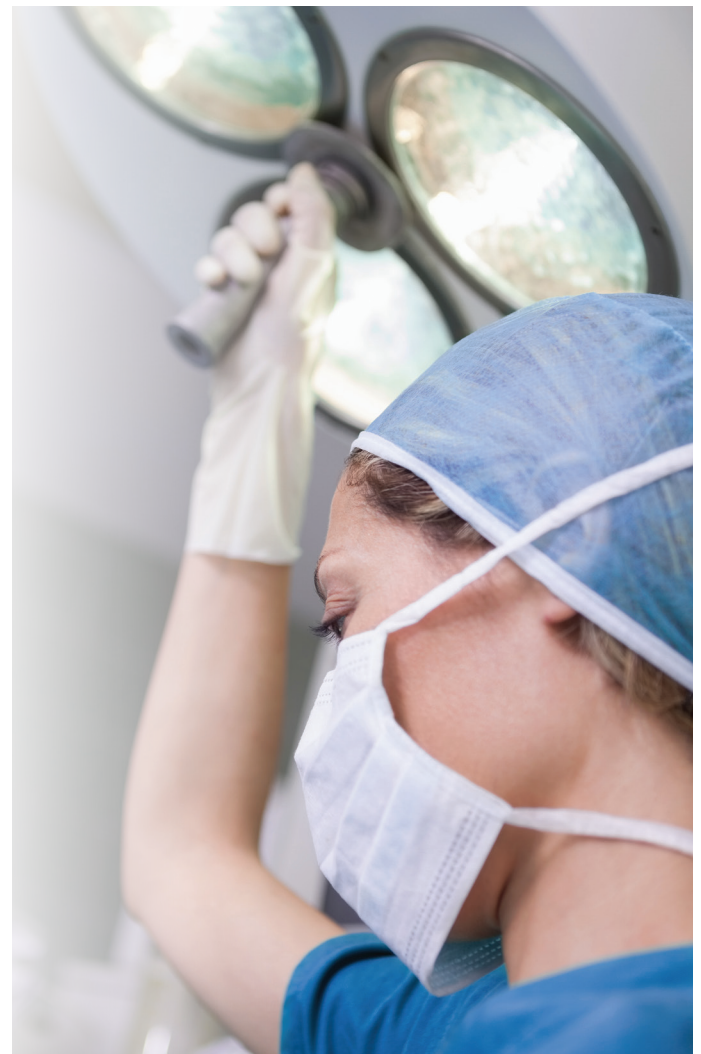
### **Agents known to cause IgG mediated or spontaneous mast cell degranulation<sup>3-9,15</sup>**

- Colloids, e.g., dextran
- Opioids, e.g., morphine

## Baseline tryptase – Guiding further mastocytosis evaluation

Raised baseline tryptase levels may be due to underlying mastocytosis. Persistently elevated baseline levels above 20 µg/l of tryptase, supported by relevant case history, should lead to the evaluation of possible mastocytosis.<sup>3-9</sup>

Total tryptase determination is recognized by the World Health Organization (WHO) as one minor diagnostic criterion of systemic mastocytosis.<sup>16,17</sup> It is commonly used in first line investigations of suspected mastocytosis.



# A proposed test algorithm – as a guide in tryptase evaluation

## Who

- Patients who have had a severe reaction during surgery.
- Patients with possible allergic reactions to drugs should be candidates for investigation and mapping of their individual tryptase levels.

## Why

- Tryptase measurement should be considered together with a thorough case history and relevant specific IgE antibody tests help to identify the underlying cause of the reaction. Importantly, this can help avoid a potentially life-threatening exposure to the offending substance.

## How

- Sample 1 (peak level): as soon as possible after the reaction (15 minutes to 3 hours).
- Sample 2 (baseline level): after complete resolution of all clinical symptoms (approx. 24 to 48 hours, or later).
- Mast cell activation is confirmed if:  $\Delta$ -tryptase (peak – baseline) is  $\geq 20\%$  of the individual's own baseline tryptase + 2  $\mu\text{g/l}$ .

**Note: The importance of measuring the transient increase of tryptase in case of severe reactions during anesthesia and surgery is well established.**<sup>5-9</sup>

## What is tryptase?

Tryptase is an enzyme and is the most abundant protein in mast cells. Within the mast cell, mature tryptase is stored in granules as a heparin-stabilized active tetramer.<sup>18,19</sup>

Proforms of  $\alpha$ -tryptase and  $\beta$ -tryptase are continuously released into the circulation and constitute the individual baseline tryptase level in serum or plasma. Each individual has its own unique baseline level of total tryptase, which is normally stable over time.<sup>2,18,19</sup>

### Tryptase as a diagnostic criterion in systemic mastocytosis

The baseline level of tryptase in the circulation reflects the number of mast cells. A persistently elevated baseline level of tryptase above 20  $\mu\text{g/l}$  is an indication of possible mast cell disorders and is recognized by the WHO as one minor diagnostic criterion of systemic mastocytosis.<sup>16,17</sup>

### Tryptase as a marker for mast cell activation

Human mast cells play a central role in inflammatory processes and in severe reactions such as anaphylaxis. When mast cells are activated, e.g., during IgE mediated allergic reactions, they release substances such as histamine and tryptase into the local surrounding tissues and the blood. Histamine is a well-known mediator causing allergic symptoms.<sup>2,18,19</sup>

While the rapid degradation of histamine makes it impractical as a marker for mast cell activation, tryptase remains stable and functional for several hours. This robustness of tryptase makes it a useful tool for confirming mast cell involvement in severe reactions like anaphylaxis. As the serum baseline tryptase level is stable over time, comparisons can easily be made between peak and baseline values.<sup>2,18,19</sup>

### Post mortem

An elevated tryptase level has been described in patients in whom death appeared to be due to anaphylaxis. To determine if this is the case, tryptase should be measured close to the time of death, and possibly at certain intervals thereafter.<sup>20</sup>

# ImmunoCAP Tryptase test

The ImmunoCAP™ Tryptase test measures the total level of tryptase released by mast cells into the circulation. This enables the measurement of transient increases in the level of tryptase after an anaphylactic reaction, as well as establishment of the person's baseline tryptase level. The ImmunoCAP Tryptase test measures all forms of tryptase.

## Collecting a sample

The measuring range is 1–200 µg/l and the amount of serum or plasma needed per test is 40 µl. Both serum and plasma samples from venous blood can be used. There is no need for special procedures when collecting blood or preparing the samples.

## Timing

### To confirm mast cell activation:

Blood samples should be collected as close to the reaction as possible, between 15 minutes and 3 hours after the onset of anaphylactic symptoms. Elevated tryptase levels can usually be detected up to 6 hours following an anaphylactic reaction and return to baseline levels approximately 24–48 hours after complete resolution of all clinical symptoms.<sup>2,10</sup>

### To measure baseline level:

Blood samples can be collected any time (before or after) outside the period of an acute reaction as described above.<sup>1</sup>

*Limitations of procedure – please refer to limitations contained in Directions for Use.*



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