INTRODUCTION

Anaphylaxis is a clinical syndrome resulting from exposure to various classes of triggers, which can vary according to the clinical setting. Thus, triggering agents in tertiary care hospital settings may differ from those in the community. Jerschow, et al. reported that fatal anaphylaxis was more frequently triggered by food in outpatients, whereas drug-induced anaphylaxis occurred more frequently in hospitalized inpatients. Furthermore, etiologic agents of anaphylaxis in hospitals have changed substantially over time, in concert with the dramatic evolution of pharmacotherapy for human diseases.

The diagnosis of anaphylaxis is based on suggestive clinical symptoms, an acceptable temporal relationship between symptom onset and exposure to a plausible trigger, and the exclusion of other possible causes of shock. As patients in general hospitals frequently have underlying diseases that could lead to sudden onset of shock, the diagnosis of anaphylaxis sometimes remains difficult in hospitals. Therefore, surveying frequent causes of anaphylaxis, as well as obtaining objective laboratory confirmation of anaphylaxis, provides important information.

Causes and Diagnostic Usefulness of Tryptase Measurements for Anaphylaxis in a Korean Tertiary Care General Hospital

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Purpose: The causes of anaphylaxis in a general hospital may differ from those occurring in a community setting. Underlying diseases in admitted patients and vague presenting symptoms can make the diagnosis of anaphylaxis difficult. Serum tryptase measurements may provide valuable evidence for diagnosing anaphylaxis in admitted patients.

Materials and Methods: This study was designed as a retrospective study of 53 patients with an anaphylaxis episode at a Korean tertiary care general hospital. Tryptase levels were measured at baseline and different time points from the onset of anaphylaxis.

Results: Drugs (42 cases; 79.2%) and foods (10 cases; 18.9%) were the most common causes of anaphylaxis. In drug-induced anaphylaxis, antibiotics (24.5%), anticancer medications, which included monoclonal antibodies (22.6%), and contrast agents (11.3%) were the most frequent causes. The muscle relaxant eperisone (5.7%), neuromuscular blocking agent rocuronium (5.7%), and its antagonist sugammadex (3.8%) were other frequent triggering agents. Wheat-dependent exercise-induced anaphylaxis was the most common entity in food-induced anaphylaxis. Tryptase concentrations were higher in patients with higher grades of anaphylaxis, as well as in accidental anaphylaxis, compared to meticulously provoked anaphylaxis. Overall diagnostic sensitivity was higher for tryptase algorithm criteria (≥[1.2×baseline+2] µg/L: 71.4%) than for abnormal tryptase level criteria (≥11.4 µg/L: 52.8%).

Conclusion: The triggers of anaphylaxis in a Korean tertiary care hospital were diverse, including beta-lactam antibiotics, anticancer medications, contrast medias, eperisone, nonsteroidal anti-inflammatory drugs, rocuronium, sugammadex, and wheat. Tryptase measurements provided valuable evidence for diagnosis, and the sensitivity of algorithm criteria was superior to that of the abnormal value criteria.

Key Words: Anaphylaxis, tryptase, drug allergy, food allergy
for diagnosing anaphylaxis in hospital settings.

Anaphylaxis is triggered primarily by an IgE-mediated allergen, which leads to degranulation of mast cells. Tryptase is a serine protease released from mast cells during an acute allergic reaction. Tryptase levels are an established indicator of mast cell activation in anaphylaxis, systemic mastocytosis, and myeloproliferative diseases, although nonspecific elevation can also occur in patients with chronic renal failure. Laboratory tests for serum total tryptase levels are frequently utilized for confirming anaphylaxis, and the Thermo Fisher ImmunoCAP tryptase assay is the golden standard for this purpose. This assay measures total tryptase concentration, including α-protryptase, β-protryptase, and mature tryptase. The normal range of basal serum total tryptase is <11.4 µg/L, in accordance with data from the manufacturer (Thermo Fisher). However, many anaphylaxis patients have levels below the upper normal value during an acute episode. Consequently, the World Allergic Association and the Consensus of the 2010 Working Conference on Mast Cell Disorders has recommended algorithm criteria for diagnosing anaphylaxis, which requires measuring tryptase levels at two time points: 1) 15 minutes to 3 hours after symptom onset and 2) at baseline, which is either before or at least 24 hours after complete resolution of all anaphylaxis symptoms and signs. The algorithm criteria define clinically significant mast cell degranulation as an acute increase in serum total tryptase level to at least (1.2×serum baseline tryptase+2) µg/L. Some studies have indicated that tryptase can be utilized as a biomarker to characterize the severity of anaphylaxis.

However, the role of tryptase measurement in allergen provocation test is not clear. Sometimes, we perform allergen provocation test for establishing the causal relationship of suspected allergen and anaphylaxis. As we gradually increase the exposure amount of suspected allergens, provocation tests frequently induce mild allergic reactions or equivocal findings, which may lead to difficulties in establishing the causal relation.

Based on the above considerations, the primary objective of this study was to identify the current etiologic agents of anaphylaxis in a Korean tertiary care hospital. The secondary objective was to evaluate the clinical role of serum tryptase measurements during an acute episode and after symptoms recover as a tool to objectively diagnose anaphylaxis reactions in various clinical situations.

MATERIALS AND METHODS

Study population
This retrospective study included 53 patients from Severance Hospital who experienced anaphylaxis from May 2019 through November 2021. The diagnosis of anaphylaxis was based on European Academy of Allergy and Clinical Immunology criteria. Patients fulfilling these criteria and who had at least one tryptase serum measurement during the anaphylaxis episode were included. Of these, 21 also had a baseline tryptase level measured as recommended by the manufacturer, allowing assessment of the algorithm criteria. This study was approved by the Institutional Review Board of Yonsei University Health System (Approval no. 4-2017-1256).

Data collection
Information regarding age, sex, atopic history, underlying disorders, and anaphylaxis triggers were collected for each patient. Clinical symptoms during the episode of anaphylaxis, including cutaneous, gastrointestinal, respiratory, and cardiovascular systems were also documented. The severity score was graded using the four-class scale modified from Ring and Messmer.

Serum tryptase concentration
Serum total tryptase concentrations were measured using the UniCAP-Tryptase fluoroimmunoassay (Thermo Fisher Science Phadia Laboratory System, Uppsala, Sweden), following the manufacturer's instructions. Two positive criteria for diagnosis of anaphylaxis were used. First criterion based on abnormally ranged value. If the serum tryptase concentration during the episode was higher than 11.4 µg/L, it was considered elevated. Second criterion was based on algorithm. If the concentration was higher than (1.2×serum baseline tryptase+2) µg/L, it was considered elevated. Following the onset of symptoms, time points for tryptase measurement were classified as 15 minutes–2 hours (T15min–2h), 2–4 hours (T2–4h), 12 hours (T12h), and 24 hours (T24h). The baseline measurement was obtained more than 24 hours after the complete resolution of all symptoms and signs or before provocation testing. Blood samples were maintained at room temperature and centrifuged for 5 min at 2500 g. Serum samples were stored at -70°C until measurement of tryptase levels.

Statistical analysis
Data were analyzed with SPSS version 26 (IBM Corp., Armonk, NY, USA). Categorical data are reported as numbers (percentage) and were compared using the χ² test or Fisher’s exact test. Continuous variables are reported as means±standard deviations. Tryptase concentrations were compared among time points using one-way ANOVA. Tryptase concentrations at T15min–2h were compared between severity grades using the nonparametric Kruskal-Wallis test. Tryptase concentrations between provocation test-induced anaphylaxis and accidental anaphylaxis were compared using Mann-Whitney U tests. P values<0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics
Patient demographics and clinical characteristics are summa-
The majority of anaphylaxis reactions were caused by drugs (79.2%), whereas a much smaller percentage was caused by foods (18.9%). Anaphylaxis was accidental in 39 cases (73.5%) and triggered by a provocation test used to confirm the diagnosis and causal relation of anaphylaxis in 14 patients (26.5%). Fourteen patients had a personal history of allergic diseases, as follows: drug allergy except contrast media (7.5%), asthma (5.7%), contrast media allergy (5.7%), allergic rhinitis (3.8%), and atopic dermatitis (3.8%). The most common diagnosis for hospital admission was cancer (43.4%), followed by a respiratory disorder, such as pneumonia (5.7%).

Anaphylaxis triggers
Specific triggers of anaphylaxis are shown in Table 2. In drug-induced anaphylaxis, the most frequent causes were antibiotics (24.5%), anticancer medications (22.6%), which included low molecular chemical agents and monoclonal antibodies, and iodide- or gadobutrol-based contrast agents (11.3%). Among the 12 anticancer medications that induced anaphylaxis, 5 cases were due to monoclonal antibodies. Other commonly identified triggers were the muscle relaxant eperisone (5.7%), rocuronium (a neuromuscular blocking agent; 5.7%), and sugammadex (a rocuronium/vecuronium antagonist; 3.8%). Among the nine cases of food-induced anaphylaxis, wheat-dependent exercise-induced anaphylaxis (6 cases) was the most common entity, followed by anaphylaxis triggered by cow’s milk (2 cases) and walnuts (1 case).

Serum tryptase concentrations and clinical severity
Serum tryptase concentrations at different time points are shown in Fig. 1. As expected, concentrations were significantly higher at T15min–2h than those at T12h ($p=0.016$), T24h ($p=0.005$) and at baseline ($p=0.005$). Tryptase concentrations at T2–4h were also higher than those at T24h ($p=0.049$) and at baseline ($p=0.046$). Fig. 2 shows the serum tryptase levels at T15min–2h according to Ring and Messmer’s anaphylaxis severity grade. Levels were higher in grade 3 anaphylaxis ($p=0.022$).

### Table 1. Demographic Features of the Enrolled Patients (n=53)

| Characteristics      | Number (%) |
|----------------------|------------|
| Sex                  |            |
| Male                 | 24 (45.3)  |
| Female               | 29 (54.7)  |
| Age                  |            |
| <18 years            | 2 (3.8)    |
| 18–65 years          | 31 (58.5)  |
| >65 years            | 20 (37.7)  |
| Etiology of anaphylaxis |          |
| Drug                 | 42 (79.2)  |
| Food                 | 9 (17.0)   |
| Idiopathic           | 2 (3.8)    |
| Cause of anaphylaxis |            |
| Accidental           | 39 (73.5)  |
| Provocation test     | 14 (26.5)  |
| Food                 | 7 (50.0)   |
| Drug                 | 7 (50.0)   |
| Antibiotic           | 3 (42.9)   |
| Muscle relaxant      | 2 (28.5)   |
| NSAID                | 2 (28.5)   |
| Personal history of atopy |        |
| Asthma               | 3 (5.7)    |
| Drug allergy         | 4 (7.5)    |
| Contrast media allergy | 3 (5.7)  |
| Allergic rhinitis    | 2 (3.8)    |
| Atopic dermatitis    | 2 (3.8)    |
| Admission diagnosis  |            |
| Cancer               | 23 (43.4)  |
| Respiratory diseases | 3 (5.7)    |
| Others               | 17 (32.1)  |

NSAID, nonsteroidal anti-inflammatory drug.

### Table 2. Specific Anaphylaxis Triggers (n=53)

| Triggers          | Number (%) |
|-------------------|------------|
| Drugs             |            |
| Anticancer medications | 12 (22.6) |
| Platinum         | 6 (11.3)   |
| Paclitaxel       | 1 (1.9)    |
| Erbitux          | 3 (5.7)    |
| Atezolizumab     | 1 (1.9)    |
| Pertuzumab       | 1 (1.9)    |
| Radiocontrast    | 6 (11.3)   |
| Iodides          | 5 (9.4)    |
| Gadovist         | 1 (1.9)    |
| Antibiotics      | 13 (24.5)  |
| Teicoplanin      | 2 (3.8)    |
| Intravenous cephalosporins | 3 (5.7) |
| Cefaclor         | 3 (5.7)    |
| Piperacillin/tazobactam | 3 (5.7)  |
| Amoxicillin      | 1 (1.9)    |
| Levofloxacin     | 1 (1.9)    |
| Muscle relaxant  | 3 (5.7)    |
| NM blocker       | 3 (5.7)    |
| Rocuronium       | 3 (5.7)    |
| NM blocker antagonist |        |
| Sugammadex       | 2 (3.8)    |
| NSAIDs           | 2 (3.8)    |
| Naproxen         | 1 (1.9)    |
| Aspirin          | 1 (1.9)    |
| Vitamin K        | 1 (1.9)    |
| Foods            |            |
| Wheat            | 6 (11.3)   |
| Cow’s milk       | 2 (3.8)    |
| Walnut           | 1 (1.9)    |

NM, neuromuscular; NSAID, nonsteroidal anti-inflammatory drug.
and grade 4 anaphylaxis ($p=0.028$) than in grade 1 anaphylaxis. Moreover, tryptase concentrations were higher with higher grade severity, with a positive correlation between severity and serum tryptase ($p=0.015$; $r=0.352$).

**Anaphylaxis triggered by provocation tests and comparisons with accidental anaphylaxis**

Among the 14 patients with anaphylaxis triggered by a provocation test, 7 were precipitated by drug provocation, and the other 7 were triggered by a food provocation test. Antibiotics (3 cases) were the most commonly provoked drug agents, followed by eperisone (2 cases) and nonsteroidal anti-inflammatory drugs (NSAIDS; 2 cases). Wheat (5 cases) was the most common culprit allergen in the 7 food provocation tests (Table 1).

Anaphylaxis severity grade was higher with accidental anaphylaxis than with provocation test–induced anaphylaxis (Table 3). Moreover, as shown in Fig. 3, tryptase concentrations at T15min–2h were significantly higher in the accidental anaphylaxis group than in the provocation test group ($p=0.019$). Although anaphylaxis was not severe in any patient with anaphylaxis precipitated by a provocation test, the median tryptase concentration was substantially higher at T1h than at baseline in the 13 patients with a positive oral provocation test ($p=0.002$) (Fig. 4). But only 4 from 14 provocation positive patients had higher concentration than 11.4 µg/L (Table 4).

**Comparison of tryptase criteria for diagnosis of anaphylaxis**

The diagnostic performances of the algorithm criteria ($\geq [1.2 \times \text{baseline tryptase}+2] \mu\text{g/L}$) and the manufacturer’s abnormal value criteria (trypetase$\geq 11.4 \mu\text{g/L}$) were compared. Overall, the diagnostic sensitivity of the algorithm criteria (71.4%) was higher than that of the abnormal value criteria (52.8%). The algorithm criteria were especially useful in provocation tests; it diagnosed four additional cases that were not identified using...
The sensitivity of the abnormal value criteria was based on data for all 53 patients. The sensitivity of the algorithm criteria was based on data for 21 patients with an available baseline tryptase measurement. The sensitivity of the abnormal value criteria was (sensitivity %) 27/39 (69.2) and the algorithm criteria was (sensitivity %) 24/39 (61.5). Table 4. Comparison of Tryptase Criteria for Diagnosing Anaphylaxis

| Criteria      | Accidental (sensitivity %) | Provocation test (sensitivity %) | Overall (sensitivity %) |
|---------------|-----------------------------|---------------------------------|-------------------------|
| Abnormal value| 24/39 (61.5)                | 4/14 (28.6)                     | 28/53 (52.8)            |
| Algorithm     | 7/8 (87.5)                  | 8/13 (61.5)                     | 15/21 (71.4)            |

The sensitivity of the abnormal value criteria was (sensitivity %) 27/39 (69.2) and the algorithm criteria was (sensitivity %) 24/39 (61.5). Table 4. Comparison of Tryptase Criteria for Diagnosing Anaphylaxis

The sensitivity of the abnormal value criteria was based on data for all 53 patients. The sensitivity of the algorithm criteria was based on data for 21 patients with an available baseline tryptase measurement.

**DISCUSSION**

This is the first study to evaluate anaphylaxis with serial serum tryptase determinations during an acute episode and after symptom recovery in Korea. This study showed that drugs were the most common triggers of anaphylaxis in a Korean tertiary care university hospital, which was consistent with the results of previous studies. Previous studies have recommended that serum samples be obtained within 1–2 hours of symptom onset to measure tryptase. This study supports the time frame of within the first 2 hours after symptom onset as the window of opportunity for good diagnostic sensitivity, after which sensitivity declines rapidly. Other investigators have reported positive correlations between tryptase levels and anaphylaxis severity, and our results also showed a similar association between severity grade of anaphylaxis and tryptase concentrations.

We also found that severity grade and peak tryptase levels were higher in accidental anaphylaxis episodes than in those induced by provocation tests. These findings may be attributed to the measured approach adapted by provocation tests, resulting in mild degrees of anaphylaxis.

Notable increments in tryptase levels have been seen following controlled drug challenges. However, the negative predictive value of tryptase measurement is not high, and the supporting evidence for this measurement in drug provocation tests is limited. Notable increments in tryptase levels have been seen following controlled drug challenges. However, the negative predictive value of tryptase measurement is not high, and the supporting evidence for this measurement in drug provocation tests is limited. Some authors have reported a significant increase in serum tryptase after drug provocation in patients with anaphylaxis, whereas others have expressed doubt about the usefulness of serum tryptase measurements in milder responses. In this study, we found that the diagnostic sensitivity of the algorithm criteria was superior to that of the abnormal level criteria for drug provocation tests. Four cases of provocation test-positive anaphylaxis did not meet the diagnostic criteria of abnormal values but did meet the algorithm criteria. Patients often experience only subjective symptoms or minimal objective symptoms in response to provocation tests, and in these cases, the algorithm criteria could be especially useful. Many guidelines recommend the algorithm criteria for diagnosing anaphylaxis instead of the abnormal value criteria. In the current study, the mean baseline tryptase concentration was 4.2 µg/L. Based on the algorithm, if the baseline value is 4.2 µg/L in a specific patient, this means that a tryptase value ≥7.04 µg/L, which is about half the of the normal value cri-
Tryptase Measurements for Anaphylaxis

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AUTHOR CONTRIBUTIONS

Conceptualization: Jung-Won Park. Data curation: Lin Liang, Kyung Hee Park, and Jae-Hyun Lee. Formal analysis: Lin Liang. Funding acquisition: Jung-Won Park. Investigation: Jung-Won Park and Lin Liang. Methodology: Lin Liang, Kyung Hee Park, and Jung-Won Park. Project administration: Jung-Won Park and Kyung Hee Park. Resources: Jung-Won Park. Software: Lin Liang. Supervision: Jung-Won Park. Validation: Jung-Won Park. Visualization: Lin Liang. Writing—original draft: Lin Liang. Writing—review & editing: Jung-Won Park. Approval of final manuscript: all authors.

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