Original Article

Yonsei Med J 2022 Dec;63(12):1099-1105
https://doi.org/10.3349/ymj.2022.0172

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

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

Lin Liang[1,2], Kyung Hee Park[2,3], Jae-Hyun Lee[2,3], and Jung-Won Park[2,3]

[1]Graduate School of Medicine, [2]Institute of Allergy, and [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

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

INTRODUCTION

Anaphylaxis is a clinical syndrome resulting from exposure to various classes of triggers,[1,2] 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.[3] 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.[1] 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.[4] Therefore, surveying frequent causes of anaphylaxis, as well as obtaining objective laboratory confirmation of anaphylaxis, provides important information

Received: May 18, 2022 **Revised:** August 20, 2022
Accepted: September 19, 2022 **Published online:** October 17, 2022
Corresponding author: Jung-Won Park, MD, PhD, Institute of Allergy and Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: parkjw@yuhs.ac

•The authors have no potential conflicts of interest to disclose.

for diagnosing anaphylaxis in hospital settings.

Anaphylaxis is triggered primarily by an IgE-mediated allergen, which leads to degranulation of mast cells.[4] Tryptase is a serine protease released from mast cells during an acute allergic reaction.[5] Tryptase levels are an established indicator of mast cell activation in anaphylaxis, systemic mastocytosis, and myeloproliferative diseases,[6] 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.[7] 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).[8] 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.[7] 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.[9] Some studies have indicated that tryptase can be utilized as a biomarker to characterize the severity of anaphylaxis.[10,11]

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.[12] 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.[12] This study was approved by the Institutional Review Board of Yonsei University Health System (Approval no. 4-2017-1258).

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.[13]

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 use. 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.[8] Second criterion was based on algorithm. If the concentration was higher than (1.2×serum baseline tryptase+2) μg/L, it was considered elevated.[9] 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 χ^2 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-

https://doi.org/10.3349/ymj.2022.0172

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	
Eperisone	3 (5.7)
NM blocker	
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.

rized in Table 1. 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)

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

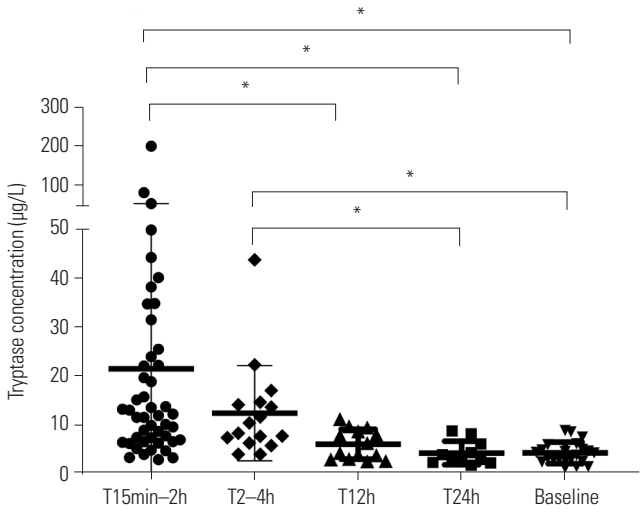

Fig. 1. Concentrations of tryptase at various times. Results are expressed as means and SD. *p<0.05.

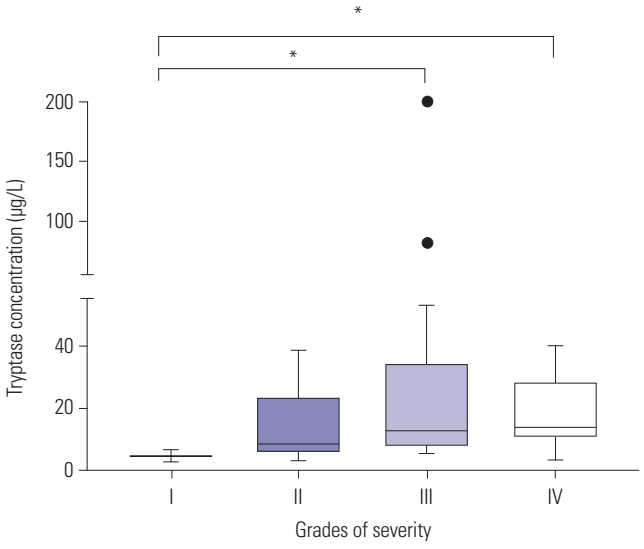

Fig. 2. Serum tryptase concentrations during anaphylaxis (T15min–2h) according to anaphylaxis severity grade. Results are expressed as a median and interquartile range. The Kruskal-Wallis test among all groups, *p<0.05.

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 (≥[1.2× baseline tryptase+2] μg/L) and the manufacturer's abnormal value criteria (tryptase≥11.4 μg/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

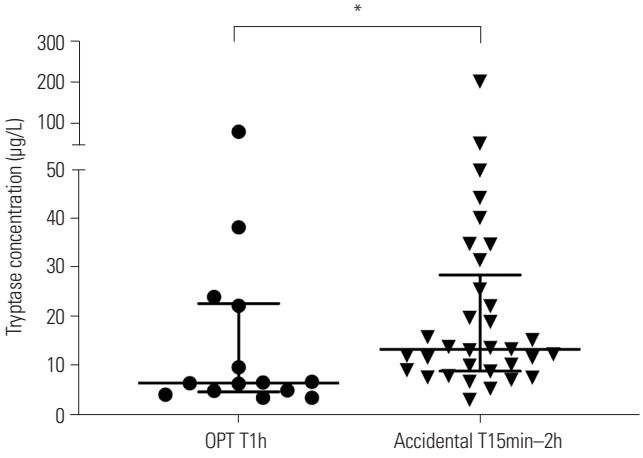

Fig. 3. Comparison of tryptase concentrations between provocation test-induced anaphylaxis and accidental anaphylaxis. Median serum tryptase values were compared using the Mann-Whitney U test. T15min–2h versus OPT T1h, Z=-2.338, p=0.019. *p<0.05.

Table 3. Grades of Anaphylaxis in Provocation Test-Induced Anaphylaxis and Accidental Anaphylaxis

Cause of anaphylaxis	n	Anaphylaxis grade				*p* value
		I	II	III	IV	
Provocation test	14	4	8	2	0	
Accidental	39	0	1	23	15	<0.001
Total	53	4	9	25	15	

https://doi.org/10.3349/ymj.2022.0172

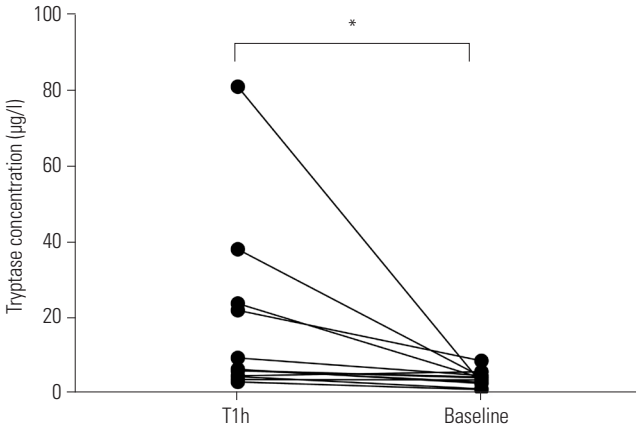

Fig. 4. Tryptase concentrations in 13 patients with positive oral provocation tests. Median serum tryptase values were compared using Wilcoxon's signed rank test. T1h versus baseline, Z=-3.040, p=0.002. *p<0.05.

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 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 abnormal value criteria (Table 4).

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.[14,15] In contrast, a prior Korean epidemiologic study based on community settings reported that bee venom was the most common trigger of anaphylaxis.[16] The discrepant results between the current study and the earlier Korean epidemiologic study may be attributed to differences in the enrolled patients. Our study was performed in patients who developed anaphylaxis during hospital admission or outpatient clinic, for which there was a clear history of potential triggers, whereas the previous epidemiologic study included cases occurring in a community setting. Precise triggers of anaphylaxis occurring in the community are frequently vague, resulting in frequent misdiagnosis of anaphylaxis and uncertain etiologies. Furthermore, the triggering agents may vary among the epidemiologic studies.[17]

In this study, antibiotics were the most frequent triggering agents, followed by anticancer medications, which included monoclonal antibodies, iodide- or gadobutrol-based contrast agents, eperisone, rocuronium, and sugammadex. These findings are similar to those of recent reports on anaphylaxis.[18-24] Food-induced anaphylaxis was relatively infrequent, occurring in only 18.9% of our study population. This may be because patients with food-induced anaphylaxis were those seen in the emergency department or undergoing provocation testing at the outpatient Allergy-Asthma Center.

Provocation tests are rarely indicated for anaphylaxis patients. However, sometimes it is inevitable for diagnosis of anaphylaxis. Eperisone and NSAID are usually co-prescribed, and provocation tests are necessary to determine the exact etiology.[22] Skin tests with or without serologic specific IgE measurement can be helpful for diagnosing beta-lactam antibiotics-induced anaphylaxis or wheat-dependent exercise-induced anaphylaxis. However the negative predictive values of these tests are unclear, and antibiotics are usually co-prescribed with NSAIDs. Thus, measured-approach provocation tests may be necessary to determine the etiologic agent.

Previous studies have recommended that serum samples be obtained within 1–2 hours of symptom onset to measure tryptase.[25,26] 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.[11,27] 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.[28,29] However, the negative predictive value of tryptase measurement is not high, and the supporting evidence for this measurement in drug provocation tests is limited.[30] 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.[31] 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.[11,32] 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 abnormal value cri-

teria, supports the diagnosis of anaphylaxis.

This study has several limitations that deserve consideration. First, as this was a retrospective study, it may have been subject to selection bias. In particular, the enrolled patients were recruited from a tertiary care general hospital, many of whom were admitted for anticancer chemotherapy, which inevitably led to emphasis on anticancer drugs as the etiology of anaphylaxis. Second, baseline levels of tryptase were not measured in all patients, which limited the power of our results.

In conclusion, the triggers of anaphylaxis in a Korean tertiary care general hospital are diverse. In addition to well recognized causes of anaphylaxis, such as beta-lactam antibiotics, NSAIDs, and wheat, various anticancer monoclonal antibodies, the muscle relaxant eperisone, neuro-muscular blocker rocuronium, and its antagonist (sugammadex) were also frequent causes of anaphylaxis in a Korean tertiary care general hospital. Serum total tryptase levels reflect the severity grade of anaphylaxis, and the diagnostic sensitivity of the algorithm criteria is superior to that of the abnormal value criteria in various clinical situations, including provocation tests.

ACKNOWLEDGEMENTS

This study was supported by the Seoul R&D Program (BT 190014) through the Research and Development for Regional Industry.

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.

ORCID iDs

Lin Liang https://orcid.org/0000-0002-7753-7004
Kyung Hee Park https://orcid.org/0000-0003-3605-5364
Jae-Hyun Lee https://orcid.org/0000-0002-0760-0071
Jung-Won Park https://orcid.org/0000-0003-0249-8749

REFERENCES

1. Simons FE. Anaphylaxis pathogenesis and treatment. Allergy 2011;66 Suppl 95:31-4.
2. Yu JE, Lin RY. The epidemiology of anaphylaxis. Clin Rev Allergy Immunol 2018;54:366-74.
3. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. J Allergy Clin Immunol 2014;134:1318-28.e7.
4. Waterfield T, Dyer E, Wilson K, Boyle RJ. How to interpret mast cell tests. Arch Dis Child Educ Pract Ed 2016;101:246-51.
5. Vitte J. Human mast cell tryptase in biology and medicine. Mol Immunol 2015;63:18-24.
6. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987;316:1622-6.
7. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World Allergy Organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472.
8. Thermo Fisher Scientific Inc. ImmunoCAP tryptase. Directions for use [Internet] [accessed on 2021 February 18]. Available at: https://dfu.phadia.com/Data/Pdf/56cb2b8a89c23251d0d2c1de.pdf.
9. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.
10. Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SG; Emergency Department Anaphylaxis Investigators. Elevated serum cytokines during human anaphylaxis: identification of potential mediators of acute allergic reactions. J Allergy Clin Immunol 2009;124:786-92.e4.
11. Vitte J, Amadei L, Gouitaa M, Mezouar S, Zieleskiewicz L, Albanese J, et al. Paired acute-baseline serum tryptase levels in perioperative anaphylaxis: an observational study. Allergy 2019;74:1157-65.
12. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: anaphylaxis (2021 update). Allergy 2022;77:357-77.
13. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977;1:466-9.
14. Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al. World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol 2013;162:193-204.
15. Wood RA, Camargo CA Jr, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol 2014;133:461-7.
16. Cho H, Kim D, Choo Y, Park J, Choi J, Jang D, et al. Common causes of emergency department visits for anaphylaxis in Korean community hospitals: a cross-sectional study. Medicine (Baltimore) 2019;98:e14114.
17. Lieberman PL. Idiopathic anaphylaxis. Allergy Asthma Proc 2014;35:17-23.
18. Brereton A, Russell WJ. Anaphylaxis to muscle relaxants: an audit of ten years of allergy testing at the Royal Adelaide Hospital. Anaesth Intensive Care 2012;40:861-6.
19. Raisch DW, Garg V, Arabyat R, Shen X, Edwards BJ, Miller FH, et al. Anaphylaxis associated with gadolinium-based contrast agents: data from the Food and Drug Administration's Adverse Event Reporting System and review of case reports in the literature. Expert Opin Drug Saf 2014;13:15-23.
20. Castells MC. Anaphylaxis to chemotherapy and monoclonal antibodies. Immunol Allergy Clin North Am 2015;35:335-48.
21. Sim DW, Park KH, Park HJ, Son YW, Lee SC, Park JW, et al. Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea. Pharmacoepidemiol Drug Saf 2016;25:1279-86.
22. Park KH, Lee SC, Yuk JE, Kim SR, Lee JH, Park JW. Eperisone-induced anaphylaxis: pharmacovigilance data and results of allergy testing. Allergy Asthma Immunol Res 2019;11:231-40.
23. Ye YM, Kim MK, Kang HR, Kim TB, Sohn SW, Koh YI, et al. Predictors of the severity and serious outcomes of anaphylaxis in Korean adults: a multicenter retrospective case study. Allergy Asthma Immunol Res 2015;7:22-9.

https://doi.org/10.3349/ymj.2022.0172

24. Jeong K, Ye YM, Kim SH, Kim KW, Kim JH, Kwon JW, et al. A multicenter anaphylaxis registry in Korea: clinical characteristics and acute treatment details from infants to older adults. World Allergy Organ J 2020;13:100449.
25. Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Clin Exp Allergy 2010;40:15-31.
26. Sheldon J, Philips B. Laboratory investigation of anaphylaxis: not as easy as it seems. Anaesthesia 2015;70:1-5.
27. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol 2013;160:192-9.
28. Cahill KN, Murphy K, Singer J, Israel E, Boyce JA, Laidlaw TM. Plasma tryptase elevation during aspirin-induced reactions in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2019;143:799-803.e2.
29. Lee JH, Lee WY, Yong SJ, Shin KC, Lee MK, Kim CW, et al. A case of levofloxacin-induced anaphylaxis with elevated serum tryptase levels. Allergy Asthma Immunol Res 2013;5:113-5.
30. Brockow K. Detection of drug-specific immunoglobulin E (IgE) and acute mediator release for the diagnosis of immediate drug hypersensitivity reactions. J Immunol Methods 2021;496:113101.
31. Komericki P, Arbab E, Grims R, Kränke B, Aberer W. Tryptase as severity marker in drug provocation tests. Int Arch Allergy Immunol 2006;140:164-9.
32. Egner W, Cook TM, Garcez T, Marinho S, Kemp H, Lucas DN, et al. Specialist perioperative allergy clinic services in the UK 2018: results from the Royal College of Anaesthetists Sixth National Audit Project (NAP6) investigation of perioperative anaphylaxis. Clin Exp Allergy 2018;48:846-61.