Management of Anaphylaxis in Dental Practice

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Anaphylaxis is a potentially fatal systemic complication that can occur as a side effect of dental treatment, oral and intravenous sedation, and general anesthesia. Although anaphylaxis rarely occurs during dental treatment, once it develops, the signs and symptoms progress rapidly and may lead to upper airway obstruction, respiratory distress, cardiovascular collapse, and cardiac arrest; thus, a prompt response is critical for saving lives. When anaphylaxis develops in a dental office, it should be diagnosed and managed immediately. Based on the clinical findings, emergency medical services should be activated and epinephrine administered intramuscularly without hesitation followed by transportation to a hospital facility for further care. It is very important to establish a definitive diagnosis of anaphylaxis after emergent care to identify the causative agent and perform subsequent dental treatment without triggering a recurrence. This review aims to explain the different issues and necessary considerations in managing anaphylaxis in the office-based dental setting based on established guidelines and practical guides for treating anaphylaxis.

Key Words: Anaphylaxis; Basophil activation test; Dental treatment; Epinephrine (adrenaline); Serum tryptase; Skin test.

According to the World Allergy Organization (WAO) Anaphylaxis Guidance 2020, anaphylaxis is defined as "a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death."[1] Severe anaphylaxis is characterized by potentially life-threatening compromise in the airway, breathing, and/or circulation.[1] Moreover, anaphylaxis may occur without typical skin features or cardiovascular shock being present.[1]

The primary pathogenesis of anaphylaxis is an immediate immunoglobulin (Ig) E-mediated allergic reaction. It is impractical to measure IgE during actual clinical diagnosis, and it is difficult to determine an IgE-mediated allergic reaction. For this reason, the term *anaphylactoid reaction* was often used as a broad term encompassing IgE-mediated and non-IgE-mediated reactions. However, the WAO and the European Academy of Allergy and Clinical Immunology (EAACI) have proposed a more comprehensive concept by defining anaphylaxis as "a severe, life-threatening, generalized or systemic hypersensitivity reaction" and suggested that the term *anaphylactoid reaction* should not be used.[2–4] Furthermore, according to the WAO and EAACI, the term *allergic anaphylaxis* should be used for reactions due to immunological mechanisms such as IgE-, IgG-, and immune complex-, complement-, or immune cell-mediated mechanisms, and all other reactions should be known as "nonallergic anaphylaxis."[2–4]

The lifetime prevalence of anaphylaxis is 0.3% to 5.1% worldwide.[1] Although it is a relatively rare reaction, once anaphylaxis develops, its signs and symptoms progress rapidly and can be life threatening; thus, prompt medical attention is required. Anaphylaxis often develops in the perioperative period; however, numerous cases of anaphylaxis caused by various drugs and materials used during dental treatment have been reported.[5–15] Since anaphylaxis is a rare occurrence in the general dental setting, it can be difficult to diagnose quickly and provide appropriate prompt treatment. A previous study reported that knowledge regarding anaphylaxis and the life-saving treatment of anaphylaxis was not significantly different between physicians and dentists ($P = .078$).[16] However, the proportion of dentists who knew the appropriate epinephrine doses for anaphylaxis (14%; 14/98 dentists), administration routes (40%; 39/98 dentists), and proper usage of an epinephrine autoinjector (27%; 26/98 dentists) was significantly lower than that of physicians ($P < .001$).[16] Furthermore, in an assessment

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Table 1. Drugs and Materials That May Cause Anaphylaxis During Dental Treatment.

Product	*Examples*
Drugs	Antibiotics (eg, amoxicillin and penicillin) Analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen) Antiseptics (eg, chlorhexidine) Sedatives (eg, midazolam, propofol, and dexmedetomidine) Local anesthetics (eg, preservatives [sodium metabisulfite], lidocaine, mepivacaine, prilocaine, and articaine)
Dental materials	Used in endodontics (eg, formaldehyde and sodium hypochlorite) Used in impressions (eg, alginate impression material)
Items with latex	Gloves, bite blocks, prophy polishing cups, dental rubber dams, orthodontic elastics, adhesive tape, anesthetic cartridges, bite wing tabs, impression materials containing latex, masks, and gutta percha

A variety of drugs and materials that can cause anaphylaxis are used in dental office. In particular, antibiotics, latex-containing products, and chlorhexidine are often reported to cause anaphylaxis in dental practice.

of knowledge regarding anaphylaxis involving 286 dentists, only 60% correctly answered "epinephrine" when asked the following question: "Which drug should be used as first-line treatment for anaphylaxis?"[17,18] Thirty-two percent of dentists selected the answers "antihistamines" and "corticosteroids,"[17,18] which are presently not recommended as initial treatment for anaphylaxis.[1,19,20] Furthermore, 40% of dentists did not have epinephrine on hand at their dental offices,[17,18] and only 55% (231/419 dentists) indicated (via self-assessment) that they could manage anaphylactic shock in the dental office themselves.[21] Therefore, it is necessary to ensure dentists have accurate knowledge about anaphylaxis. Hence, this review aims to discuss the necessary considerations and issues in the clinical diagnosis, initial treatment, definitive diagnosis, and identification of the causative agent in cases of anaphylaxis in a general dental office.

ANAPHYLAXIS IN THE DENTAL OFFICE

Epidemiology of Anaphylaxis

Since pain and psychological stress often occur during dental care, it is not uncommon for systemic complications to occur in patients undergoing treatment in a dental office. The most common systemic complications during dental treatment are vasovagal syncope (62%–63%), angina (12%), hypoglycemia (10%), and seizure (7%–10%); as its incidence is only 0.4% to 2.1%, anaphylaxis is considered a rare complication.[21–24] The number of cases of anaphylaxis during dental treatment encountered by a dentist is approximately 0.004 to 0.013 per year, suggesting that a dentist is likely to encounter a case of anaphylaxis once every 77 to 250 years.[23,24] This rate is extremely low compared with that for vasovagal syncope, in which the number of cases likely to be encountered by a dentist is 1.9 per year (i.e., once every 6 months).[23]

Furthermore, some dentists perform intravenous (IV) sedation and general anesthesia in the office-based setting[25]; accordingly, those providers should also know how to manage perioperative anaphylaxis. The incidence of perioperative anaphylaxis varies by region and by study. The most prominent estimated incidence is 0.01% (1 in 10 000 cases of general anesthesia), with a mortality rate of 3.8% to 4.8%, based on studies performed in the United Kingdom and France.[26–28]

Typical Causative Agents of Anaphylaxis in Dental Practice

Various drugs and materials are used in dental practice, many of which can cause anaphylaxis[5–15]; hence, care should be taken when using them (Table 1). Special attention should be observed when using antibiotics such as penicillin, pain medications such as nonsteroidal anti-inflammatory drugs, antiseptics such as chlorhexidine, and latex products in dental practice. Penicillin and amoxicillin are frequently used in dentistry. These antibiotics are classified as β-lactam antibiotics, and cross-reactivity with cephalosporins has been reported, albeit with a low probability of 2%.[29] In addition, Zagursky and Pichichero[30] reported that there is ample evidence to allow for the safe use of all but a few early-generation cephalosporins in patients with penicillin or amoxicillin allergy. They reported that the past belief that penicillin-allergic patients must avoid all cephalosporins should be dismissed as a myth.[30] Therefore, penicillin cross-reactivity may no longer be considered. In the past, performing an intradermal test using a small amount of drug before the IV administration of antibiotics was also recommended. However, this is currently not recommended owing to its poor predictive value for the onset of anaphylaxis.

In a survey of 402 people who visited an allergy clinic due to complaints of allergic reactions associated with local anesthesia, only 0.5% (2 people) had genuine and presumably IgE-mediated allergy to local anesthetics, thus indicating that anaphylaxis related to the use of local anesthetics is extremely rare.[31] It should be noted that

latex-related anaphylaxis is a concern not only for patients but also dental professionals, such as dentists and dental hygienists, who also frequently report occupation-related anaphylaxis due to latex-containing products.[32,33]

Typical Causative Agents of Anaphylaxis During General Anesthesia

A large-scale epidemiological study conducted in France reported that the major causative agents of perioperative anaphylaxis were neuromuscular blocking agents (NMBAs; 58%) used in general anesthesia, latex (20%), and antibiotics (13%).[28] The most common NMBAs that induce anaphylaxis were succinylcholine (33%), rocuronium (30%), atracurium (19%), and vecuronium (10%). Unlike adults, anaphylaxis in children aged 18 years and younger was mainly caused by latex (42%), followed by NMBAs (32%) and antibiotics (9%).[28] The 6th National Audit Project of the Royal College of Anaesthetists (NAP6), a large-scale epidemiological study conducted in the United Kingdom, reported antibiotics (47%), NMBAs (33%), and chlorhexidine (9%) as the primary causes of perioperative anaphylaxis, and the most common NMBAs were rocuronium (42%), atracurium (35%), and succinylcholine (22%).[27] In addition, penicillin antibiotics accounted for half of the antibiotic-induced perioperative anaphylaxis cases that were reported in both the French and NAP6 studies.[27,28] A Japanese survey found that NMBA-reversing sugammadex (28%), rocuronium (22%), cefazolin (17%), and other antibiotics (15%) were the major causative agents of perioperative anaphylaxis.[34] Since 64% of sugammadex-induced anaphylaxis cases are reported from Japan,[35] sugammadex, NMBAs, and antibiotics are considered the major causative agents of perioperative anaphylaxis in Japan. Based on the above findings, the main allergens that induce perioperative anaphylaxis are NMBAs and antibiotics, while latex and sugammadex are also important allergens reported in some regions.

Timing of Anaphylaxis Onset

Anaphylaxis in dental offices is caused mainly by drugs and latex-containing products used during dental treatment. As with anaphylaxis in general, the timing of onset is within several minutes to several hours after exposure to the causative agent. In general, IV administration causes an earlier onset of anaphylaxis and more severe reactions compared with oral administration. Therefore, an observational period of 15 minutes should be used when a drug is administered intravenously, and 2 hours should be used when a drug is administered orally. However, 50% of patients who experience anaphylaxis caused by endodontic disinfectant or sealant (formaldehyde) develop a reaction 2 hours or more (maximum of 12 hours) after treatment; hence, caution should be observed when using this product.[5,6]

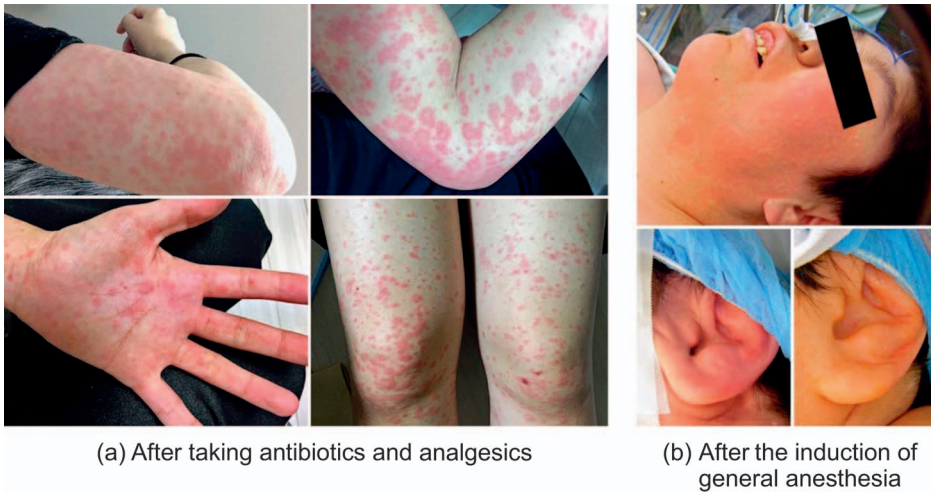
Furthermore, both Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are known as type IV (delayed) hypersensitivity reactions.[36,37] SJS and TEN can be fatal allergic reactions like anaphylaxis that are triggered by the administration of common analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs, and antibiotics.[36,37] Because SJS and TEN are delayed allergic reactions, they develop hours to days to weeks after drug administration, unlike anaphylaxis.[36] SJS and TEN show early systemic signs and symptoms, including fever, fatigue, a sore throat and mouth, cough, red eyes, and tender, pink skin ~1 to 3 days before a rash develops.[36–38] As the condition worsens, other systemic signs and symptoms include unexplained widespread skin pain, a red or purple rash that spreads, and blisters on the skin, lips, nose, eyes, and genitals. Although SJS and TEN are rare conditions, the mortality rate is 15% to 50% for TEN, 19% to 29% for SJS/TEN overlap, and 5% to 10% for SJS.[36,37] Therefore, SJS and TEN require appropriate diagnosis and management just like anaphylaxis.

Meanwhile, ~81% of perioperative anaphylaxis cases develop after anesthesia induction and before the operation's commencement.[27] This is thought to be due to the increased exposure to NMBAs, antibiotics, and latex-containing products that cause anaphylaxis when anesthesia is induced. In addition, 95% of NMBA-induced anaphylaxis cases occur within 5 minutes after IV administration,[27] 97% of antibiotic-induced anaphylaxis cases occur within 15 minutes after IV administration (74% within 5 minutes, 18% within 6–10 minutes, and 5% within 11–15 minutes),[27] and 72% to 92% of sugammadex-induced anaphylaxis cases develop within 5 minutes after IV administration.[35] Therefore, vital signs should be monitored for at least 5 minutes after the IV administration of NMBAs and sugammadex and at least 15 minutes after the IV administration of antibiotics.

Recognizing Anaphylaxis

During anaphylaxis, signs and symptoms appear throughout the body as the allergen induces the release of large amounts of histamine from mast cells and basophils via various immunological and nonimmunological mechanisms.[1] The main clinical findings of

Figure 1. Skin Involvement and Anaphylaxis



(a) Skin findings developed after the oral administration of antibiotics and analgesics following the extraction of a third molar. (b) Skin findings on the face and ears immediately developed after the induction of general anesthesia. Lower left figure: At the onset of anaphylactic shock. Lower right figure: After treatment of anaphylactic shock.

anaphylaxis are skin or mucosal (Figure 1), respiratory, cardiovascular, gastrointestinal, and central nervous system signs and symptoms (Table 2).[1] The WAO position paper published in 2020 presented the following 2 simplified criteria for diagnosing anaphylaxis[1]:

Diagnostic criterion 1: Acute onset with simultaneous involvement of skin, mucosal tissue, or both (eg, generalized hives; pruritus or flushing; swollen lips, tongue, or uvula) and at least 1 of the following: respiratory compromise, cardiovascular collapse, or severe gastrointestinal symptoms.

Diagnostic criterion 2: Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Signs and symptoms were previously thought to develop in multiple organs when anaphylaxis occurred; however, close monitoring should be performed as severe symptoms may appear in only one organ system. It has been reported that skin signs are absent in 10% to 20% of anaphylaxis reactions, which may result in delays recognizing and initially treating anaphylaxis.[1]

Table 2. Typical Signs and Symptoms of Anaphylaxis.

Clinical features	*Frequency (%)*
Skin or mucosa	80–90
Flushing, urticaria (hives), angioedema, rash, erythema, and conjunctival erythema	
Periorbital itching; itching of lips, tongue, palate, external auditory canals, genitalia, palms, and soles	
Edema; swelling of lips, tongue, or uvula	
Respiratory	Up to 70
Nasal: itching, congestion, rhinorrhea, and sneezing	
Throat: itching and tightness, dysphonia, hoarseness, stridor, and dry staccato cough	
Lower airways: chest tightness, deep cough, and wheezing or bronchospasm	
Increased respiratory rate, shortness of breath, and cyanosis; respiratory arrest	
Gastrointestinal	Up to 45
Nausea, vomiting, dysphagia, abdominal pain, and diarrhea	
Cardiovascular system	Up to 45
Chest pain and fainting spells	
Tachycardia, bradycardia (less common), arrhythmias, and palpitations	
Hypotension and shock; cardiac arrest	
Central nervous system	Up to 15
Aura of impending doom, uneasiness, altered mental status, and confusion	
Headache, dizziness, tunnel vision	
Other	Not determined
Urinary or fecal incontinence; metallic taste; cramps and bleeding due to uterine contractions	

Table 3. Considerations When Establishing a Differential Diagnosis of Anaphylaxis.

Difficult-to-differentiate disease and symptoms	*Common symptoms*	*Consideration points*
Vasovagal syncope	Hypotension	Typically relieved by supine positioning; usually associated with pallor and sweating; without urticaria, skin flushing, respiratory or gastrointestinal findings
Anxiety or panic attack	Aura of impending doom, flushing, tachycardia, shortness of breath, and gastrointestinal symptoms	Does not cause urticaria, angioedema, wheeze or stridor, or hypotension
Hyperventilation	Tachycardia, dizziness, and shortness of breath	Does not cause urticaria, angioedema, wheeze or stridor, or hypotension
Acute asthma	Cough, wheezing, shortness of breath, and cyanosis	Does not cause itching, urticarial (hives), angioedema, abdominal pain, or hypotension

When anaphylaxis is differentiated from other conditions, it is easier to make a diagnosis based on skin (eg, itching, rash), respiratory (eg, wheezing, dyspnea), and cardiovascular (eg, hypotension, tachycardia) findings.

In diagnosing anaphylaxis that develops at a dental office, patients should be observed for complaints of anxiety, dizziness, itching, dyspnea, and abdominal pain considering they are often conscious during the early stages of anaphylaxis. In addition, to correctly diagnose anaphylaxis, it should be distinguished from systemic complications that may occur during dental treatment, such as vasovagal syncope, panic or anxiety attacks, and asthma. Table 3 shows the valuable points to consider when developing a differential diagnosis.

The clinical signs and symptoms of anaphylaxis that develop during general anesthesia are not different from those proposed by the WAO, and anaphylaxis is typically diagnosed based on skin and mucosal involvement (eg, flushing; erythema; angioedema; measles-like rash; edema of the lips, tongue, and uvula; palpebral erythema or edema; conjunctival erythema; and palpebral conjunctival hyperemia), respiratory complications (eg, wheezing, bronchospasm, airway narrowing findings on capnography, decreased tidal volume during pressure-controlled ventilation, increased maximum airway pressure during volume-controlled ventilation, and hypoxemia), and cardiovascular complications (eg, rapid drop in blood pressure, tachycardia, bradycardia, arrhythmia, and Kounis syndrome [an acute coronary syndrome, such as coronary spasm and acute myocardial infarction associated with mast cell activation from hypersensitivity including anaphylaxis][39]).[4]

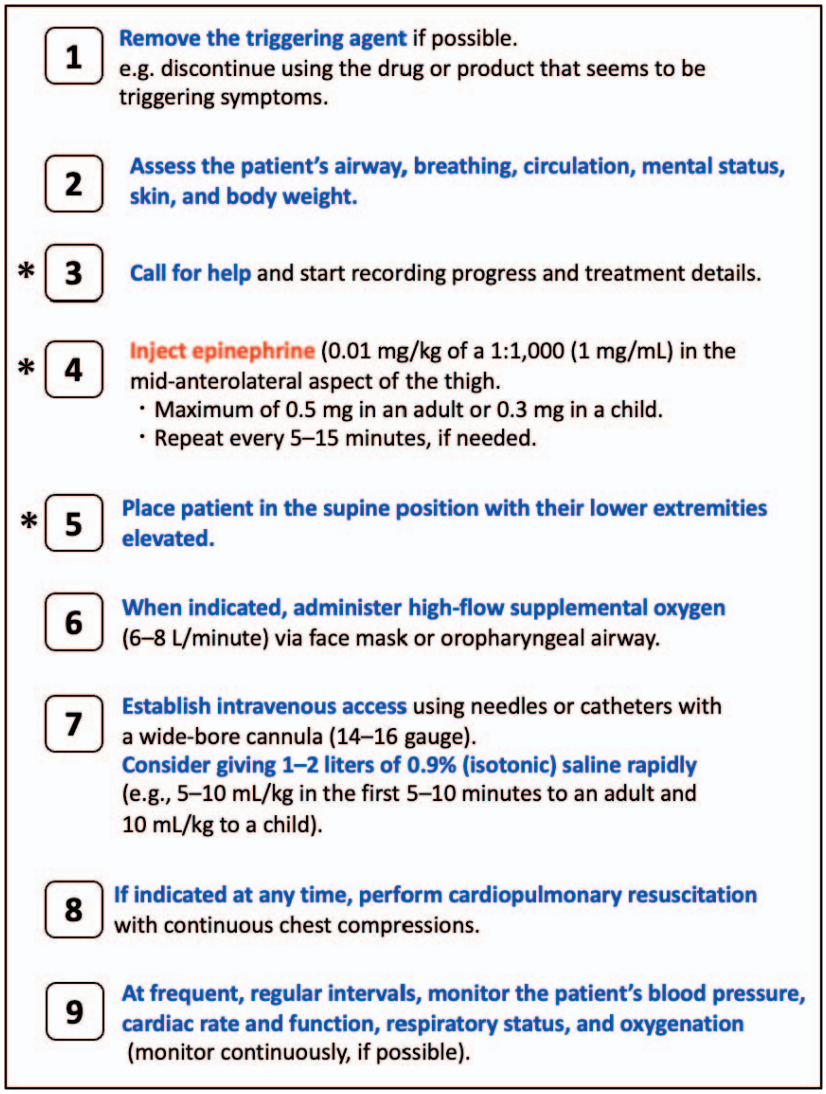
However, caution should be taken, as the early diagnosis of perioperative anaphylaxis during anesthesia can be complicated for the following reasons: (1) the patient may be unconscious and not complain of any symptoms; (2) causative drugs may affect the cardiovascular system during induction, making it difficult to discern whether the cardiovascular complications are due to anaphylaxis or the anesthetic agents; (3) it may be challenging to identify any respiratory complications before the clinical condition worsens because the patient is often intubated and possibly under mechanical ventilation; and (4) skin involvement may not be promptly observed as the patient's body is usually covered with surgical drapes while under anesthesia.

In recent years, skin involvement (flushing or rash), which usually occurs in 90% of patients who experience anaphylaxis, accounted for less than 10% of the initial findings for perioperative anaphylaxis, and rash appeared in only 56% of patients who experienced perioperative anaphylaxis.[27] In a perioperative anaphylactic case that was the first case of anaphylactic shock encountered by the present author within 7 years after becoming a dental/dentist anesthesiologist, epinephrine was administered within only 25 minutes after the onset of anaphylaxis because no skin reactions (a specific symptom of anaphylaxis) were observed, thus preventing the early diagnosis of anaphylaxis.[40] Fortunately, the patient survived the anaphylactic episode, but the delayed initial response was a major reflection point for the present author. Therefore, regardless of the presence or absence of skin symptoms, anaphylaxis should be suspected, and initial treatment for anaphylaxis should be considered and/or initiated when vasopressor-resistant shock occurs, the blood pressure suddenly drops, or airway narrowing or breathing difficulties arise whenever a triggering substance is in use.

Managing Anaphylaxis in the Dental Office

Since the incidence of anaphylaxis in dental offices is extremely low, it is difficult for all dental/dentist anesthesiologists, dental surgeons, and dentists to gain sufficient experience managing this condition. However, once signs and symptoms develop, they progress rapidly, and various treatments should be provided immediately; therefore, emergency protocols that fit each dental practice or institution should be developed and initiated at the time of anaphylaxis onset. In addition, emergency

Figure 2. Management of Anaphylaxis in the Dental Office



Anaphylaxis should be recognized at an early stage, epinephrine should be administered intramuscularly, and the patient should be transported immediately to a hospital.
*Implement steps 3–5 promptly and simultaneously.[1]

simulations should be performed regularly that include anaphylaxis and incorporate team collaboration when managing an emergency.

Initial Treatment of Anaphylaxis.[1] Figure 2 outlines the initial response at the time of anaphylaxis onset. Upon development, anaphylaxis should be promptly recognized. When a patient is diagnosed with anaphylaxis, the first step is to activate emergency medical services (EMS; ie, paramedics and ambulance). Next, potentially triggering substances (eg, drugs, dental materials, equipment or instruments, latex-containing products) should be removed, and the patient's condition should be appropriately evaluated. Assessing a patient's airway, breathing, circulation, mental status, and skin condition is essential for establishing a differential diagnosis of anaphylaxis. The patient should be placed in the supine position, and epinephrine should be administered intramuscularly, ideally in the vastus lateralis (outer thigh), at an early stage. If necessary, the patient should be given high-flow supplemental oxygen via a face mask, IV access should be established using large-bore catheters (ideally 14–16 gauge), and a transfusion of 0.9% saline (5–10 mL/kg for an adult and 10 mL/kg for a child in the first 5–10 min) should be initiated. In addition to these measures, cardiopulmonary resuscitation should be performed if indicated. Preparations should be made to secure the airway for providers capable of doing so. The patient's blood

pressure, heart rate, respiratory status, and oxygenation should be monitored closely, regularly and continuously.

Supplemental medications may include beta-2 adrenergic agonists (eg, albuterol), antihistamines, and glucocorticoids. Antihistamines relieve only skin signs and symptoms and are ineffective against cardiovascular and respiratory involvement.[19] Glucocorticoids may be effective in preventing biphasic reactions; however, they do not alleviate acute anaphylaxis and may even be harmful in younger patients.[1,19] It has been reported that children with anaphylaxis younger than 18 years who received glucocorticoids may be at an increased risk of biphasic reactions.[41] As such, the routine use of glucocorticoids is becoming controversial. Therefore, administering antihistamines and glucocorticoids as initial or primary treatment for anaphylaxis is not recommended. Antihistamines and glucocorticoids can be administered as secondary or tertiary treatment if necessary.[1,19,20,41]

Administration of Epinephrine

In cases of iatrogenic anaphylaxis, the median time from onset to cardiac arrest is 5 minutes.[42] Hence, a prompt diagnosis and timely treatment are critical for saving the patient's life when anaphylaxis occurs. In addition, an absence of skin involvement coupled with the delayed administration of epinephrine leads to fatal anaphylaxis.[43] The incidence of biphasic reactions also increases when the time from the onset of anaphylaxis to epinephrine administration exceeds 30 minutes.[44] Therefore, epinephrine should be administered early when serious cardiovascular and respiratory findings are noted, even in the absence of skin involvement. The proper administration of epinephrine is described below.

Epinephrine in the Dental Office Setting. When a patient develops anaphylaxis in a dental office, epinephrine can be safely administered via intramuscular (IM) injection, which has almost no adverse effects. When epinephrine is administered intramuscularly, it should be injected in the middle of the anterolateral thigh (vastus lateralis). The anatomical landmark for needle insertion is the midpoint of the line connecting the greater trochanter of the femur and the center of the patella with a needle depth well into the muscle tissue. The initial dose of IM epinephrine is 0.01 mg/kg (maximum dose for adults: 0.5 mg; maximum dose for children: 0.3 mg).[1] By age, the recommended doses are 0.01 mg/kg for infants weighing 10 kg or less, 0.15 mg for children aged 1 to 5 years, 0.3 mg for children aged 6 to 12 years, and 0.5 mg for teenagers and adults.[1] The blood concentration of epinephrine peaks within 10 minutes after IM administration and is reduced to half within 40 minutes after administration.[45,46] Korenblat et al[47] reported that 36% (38/105 patients) of patients who developed anaphylaxis required 2 or more doses of epinephrine. Therefore, if epinephrine is administered intramuscularly and the symptoms do not improve, IM injections should be repeated every 5 to 15 minutes.[1,19]

The transient adverse effects of IM epinephrine in adults were reported as pallor (25%; 13/52 injections), tremor (13%; 7/52 injections), heart palpitations (13%; 7/52 injections), headache (6%; 3/52 injections), and shivers and dizziness (2%; 1/52 injections)[5]; those in children included tremor (94%; 16/17 injections), pallor (82%; 14/17 injections), headache (24%; 4/17 injections), tingling of the extremities (18%; 3/17 injections), and nausea (6%; 1/17 injections).[46] However, no serious adverse effects were reported in these studies.[45,46] Therefore, epinephrine should be administered intramuscularly without hesitation. However, IM epinephrine in patients aged 60 years and older increases the incidence of cardiovascular adverse events, especially in those aged 80 years and older (odds ratio: 8.8); hence, elderly patients receiving epinephrine should be thoroughly monitored.[48] If unfamiliar with IM administration using ampule formulations, syringes, and needles, an epinephrine auto-injector (eg, EPIPEN) is recommended. The EPIPEN for adults and children can accurately, quickly, and easily administer 0.3 mg or 0.15 mg of epinephrine, respectively. Therefore, the use of an EPIPEN may eliminate overdose or underdose errors.

Epinephrine in the Perioperative Setting. Epinephrine for the treatment of perioperative anaphylaxis can be administrated intravenously or intramuscularly. The Japanese Society of Anesthesiologists Practical Guidelines recommends IV epinephrine for perioperative anaphylaxis.[4] This is probably because the IV onset of action is quicker than IM and because hemodynamic changes are easy to ascertain while a patient is being thoroughly monitored under general anesthesia. The required doses of IV epinephrine are 0.2 μg/kg at the time of hypotension, 50 to 300 μg at the time of cardiovascular collapse, and continuous IV infusion (0.05–0.1 μg/kg/min) if repeated administration is necessary.[4,49] However, it should be remembered that IV epinephrine is more likely to cause overdose (odds ratio: 61.3) and adverse events (odds ratio: 8.7) than IM epinephrine.[50] When epinephrine is administered intravenously, the present author recommends titrating 10 to 20 μg per dose as relatively safe while monitoring the patient's hemodynamics, although this depends on certain conditions, such as blood pressure. However, if a dentist is not familiar with the use of epinephrine, IM

administration is preferred, even in the perioperative period.

Monitoring After Initial Treatment of Anaphylaxis

After the onset of anaphylaxis, 0.4% to 14.7% of patients may experience biphasic reactions that lead to recurrent anaphylaxis without reexposure to the trigger.[44,51] Patients diagnosed with anaphylaxis should be monitored in a hospital for at least 6 to 8 hours if respiratory symptoms occur and for at least 12 to 24 hours if hypotension occurs.[19] Therefore, if a patient develops anaphylaxis in the dental office, they should be transported emergently to a hospital after initial treatment, regardless of the severity or potential resolution of the allergic reaction.

ANAPHYLAXIS: ESTABLISHING A DEFINITIVE DIAGNOSIS

After the acute management of anaphylaxis, establishing a definitive diagnosis and identifying the trigger are required. Therefore, dental/dentist anesthesiologists should proactively conclude a definitive diagnosis of anaphylaxis and prevent its recurrence. The definitive diagnosis of anaphylaxis has 3 important elements: (1) evaluation of clinical symptoms, (2) measurement of tryptase and histamine levels, and (3) identification of the causative agent by skin tests. Therefore, it is important to reach a definitive diagnosis based on multiple perspectives by combining these factors.[52] The accuracy of identifying causative substances can be improved by combining in vivo and in vitro tests.

The First Piece of Evidence: Assessment of Clinical Signs

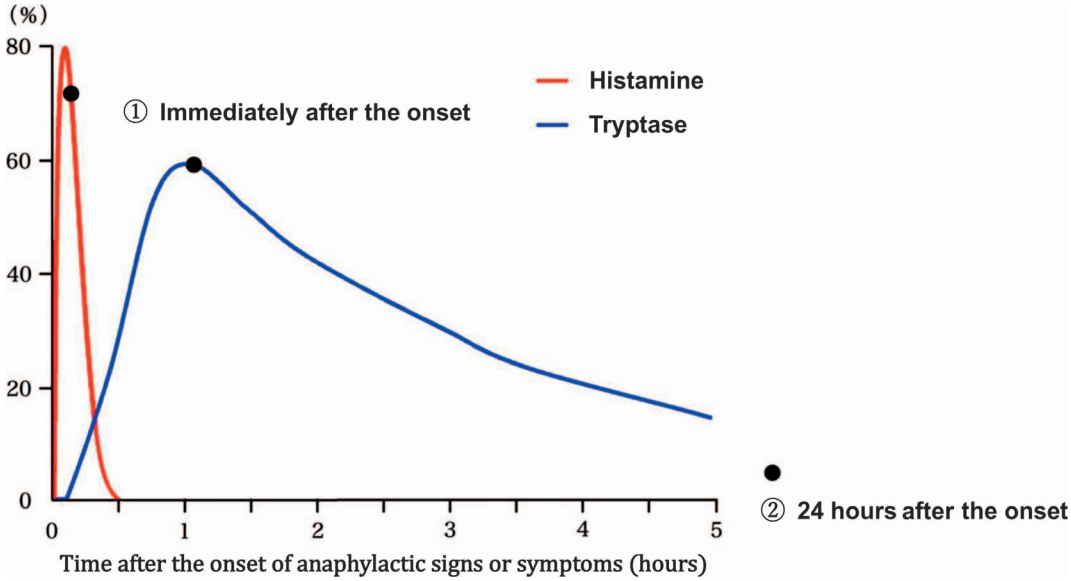
The first piece of evidence in obtaining a definitive diagnosis of anaphylaxis should include the characteristics and severity of clinical findings at the onset of the allergic reaction, the use of suspected allergens (ie, triggers), and the timing of the onset of the allergic reaction. Although various criteria for diagnosing anaphylaxis have already been established based on the clinical presentation, the present article recommends the clinical scoring system for immediate-onset allergic reactions reported by Hopkins et al,[53] which the author frequently uses. This scoring system is specialized for diagnosing perioperative anaphylaxis, and the following 5 categories are assessed: (1) cardiovascular, (2) respiratory, (3) skin or mucosal, (4) combinations, and (5) timing of onset. These categories are scored, and the total score is used to estimate the likelihood of anaphylaxis. Since specialists in immediate-type allergies created this scoring system, it is considered highly reliable and likely to help obtain an objective diagnosis of perioperative anaphylaxis. Anaphylaxis during dental treatment should be evaluated according to the diagnostic criteria proposed by the WAO as previously described.

The Second Piece of Evidence: Serum Tryptase and Histamine Levels

The second piece of evidence is obtained by collecting blood samples after the onset of anaphylaxis and measuring the serum tryptase and histamine levels to confirm the activation of mast cells and basophils. When anaphylaxis occurs, histamine and tryptase are often released from mast cells and basophils into the blood. Therefore, if anaphylaxis is suspected, blood samples should be collected to measure the histamine and tryptase levels when possible.[4] Since tryptase is relatively mast cell selective, an increase in tryptase levels in the blood directly signifies the activation of mast cells. Tryptase levels tend to elevate when anaphylaxis worsens, with median tryptase levels reported as 10.7 μg/L for class III anaphylaxis (cardiovascular collapse, tachycardia or bradycardia, cardiac arrhythmias, or bronchospasm), 66.2 μg/L for class IV (cardiac or respiratory arrest), and 200 μg/L for class V (death).[54]

Histamine levels peak 5 minutes after the onset of anaphylaxis and return to baseline levels 15 to 30 minutes after the onset; hence, blood samples should be taken within 5 to 10 minutes after the onset of anaphylaxis.[4] The WAO position paper recommends blood sampling for histamine levels within 15 to 60 minutes after the onset of anaphylaxis.[55] The plasma concentrations of tryptase increase within 30 minutes after the onset of anaphylaxis and reach a peak within 1 to 2 hours after the onset of anaphylaxis; hence, the optimum timing for blood sampling is 30 to 120 minutes after anaphylaxis onset (Figure 3).[55,56] Blood sampling within 30 minutes or after 180 minutes of onset may not show an increase in the tryptase level; therefore, care should be taken when measuring this parameter.[56] Considering the half-life of histamine, it is easier to measure the tryptase level than the histamine level; therefore, blood sampling should be performed to at least measure the tryptase level. In addition, blood sampling for histamine and tryptase should be performed at the time of anaphylaxis onset and after 24 hours, and the measured values at these 2 times should

Figure 3. Changes in Blood Concentrations of Histamine and Tryptase After the Onset of Anaphylaxis



When anaphylaxis occurs, mast cells and basophils release histamine and tryptase. To diagnose anaphylaxis, blood samples should be collected at 2 times: the onset of anaphylaxis and after 24 hours. Histamine and tryptase levels should be compared.

be compared. The activation of mast cells is indicated when the serum acute tryptase level at the onset of anaphylaxis is higher than the following calculated value [serum baseline tryptase level (value at 24 hours after onset) × 1.2 + 2].[56] This formula has a 94% positive predictive value, 53% negative predictive value, 75% sensitivity, 86% specificity, and a Youden's index value of 0.61.[57] However, anaphylaxis cannot be ruled out even when tryptase levels are not elevated. Since few studies have reported a cutoff value for histamine in diagnosing anaphylaxis, further research is warranted to explore this matter further.

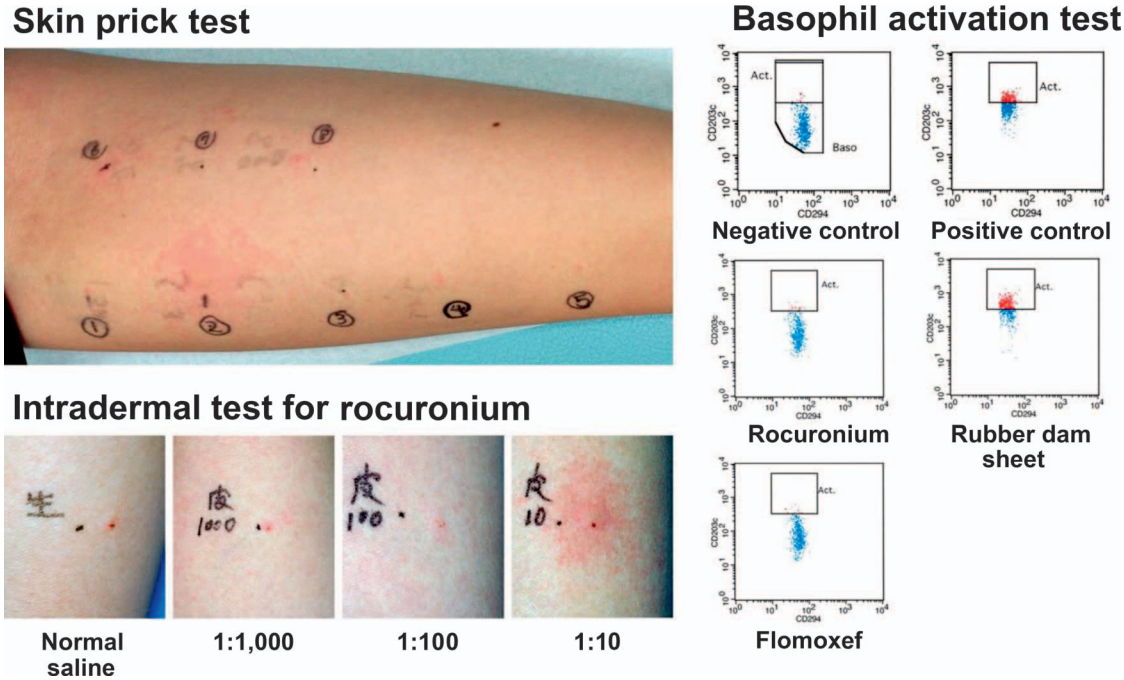
The Third Piece of Evidence: Identification of Causative Agents

The third piece of evidence is obtained using skin and blood tests to identify the causative agent of anaphylaxis (Figure 4). Currently, skin testing performed within 4 to 6 weeks after the onset of anaphylaxis is considered the gold standard for determining the causative agent.[4] However, it should be noted that the diagnostic accuracy of this method is 72.9%; it is not always 100% accurate.[58] The skin prick test (SPT) is initially performed; if the SPT result is negative, an intradermal reaction test is carried out.[4] As anaphylaxis can recur during the skin test, with incidence rates of only 0.4% for SPT and 3.2% for an intradermal test,[59] and because these tests are invasive and cause pain, many parents of pediatric patients are against using these tests. Therefore, performing a combination of in vitro tests (with less risk and burden on the patient) can make it easier to obtain the patient's cooperation in undergoing the tests and improve their diagnostic accuracy. The dilution ratios of reagents used for skin tests are provided in Australian and New Zealand guidelines, which are helpful.[60]

Since drug-induced lymphocyte stimulation testing is used only for determining class IV allergies, it is not a suitable tool for diagnosing anaphylaxis.[4] Most reagents used for allergen-specific IgE tests are foods, plants, animals, and latex, and it is difficult to use muscle relaxants during allergen-specific tests, as they frequently trigger perioperative anaphylaxis.[4] As β-lactam antibiotics do not have high sensitivity and specificity, using these drugs for routine testing is meaningless.[4]

In recent years, the basophil activation test (BAT) has attracted attention as an in vitro test for identifying the causative agent of anaphylaxis.[4,61,62] The BAT does not induce anaphylaxis recurrence, and obtaining the patient's or parent's consent for this test is easy. It is also very versatile, as it can also be tested with the products actually used during dental treatment (rubber dam sheets, etc).[63] Moreover, the BAT has high diagnostic accuracy for rocuronium (sensitivity: 92%, specificity: 100%) and sugammadex (sensitivity: 88%, specificity: 100%), likely triggers for perioperative anaphylaxis.[61,62] Accordingly, this test may be helpful for the identification of triggers of perioperative anaphylaxis. However, because of some disadvantages

Figure 4. Skin Prick and Basophil Activation Tests



Example of a skin prick test: 1. normal saline (negative control), 2. histamine (positive control), 3. fentanyl, 4. remifentanil, 5. atropine, 6. piperacillin, 7. propofol, and 8. rocuronium. All skin prick tests showed negative results. Intradermal skin test for rocuronium showed positive result at 10-fold dilution (15 minutes later, wheal: 5 × 7 mm; erythema: 25 × 22 mm). Basophil activation test showed that rocuronium and flomoxef were negative results, and a rubber dam sheet was a positive result.

of the BAT, such as the need for fresh blood samples, the need to perform the test within the recommended 4 hours after blood collection,[4] the possibility of false-negative or false-positive test results, and the small number of institutions that can perform tests requiring a flow cytometer, the results should be carefully interpreted and the findings of other skin tests should also be considered.

Simulation Training for Anaphylaxis in the Dental Office Setting

Since anaphylaxis rarely occurs during dental treatment, it is important to perform routine simulations that include the initial treatment of anaphylaxis. Kishimoto et al[64] reported that when they simulated anaphylaxis using a software application, the percentage of respondents who answered, "I can treat anaphylaxis adequately" increased from 6% to 42% before and after the simulation training. Tan[65] reported that simulation activity using a human patient simulator is an acceptable and valuable technique to help improve confidence in managing crisis situations that may occur in dental offices. Therefore, to save lives, it is important to create a protocol for anaphylaxis that suits each dental office and conduct regular simulations with all staff.

CONCLUSION

Since the signs and symptoms of anaphylaxis progress rapidly once it develops, prompt diagnosis and timely treatment are necessary in out-of-hospital settings. In such situations, regardless of the presence or absence of skin symptoms, it is important to suspect anaphylaxis, quickly activate EMS, and immediately administer appropriate doses of epinephrine if respiratory or cardiovascular symptoms are present. In addition, a definitive diagnosis of anaphylaxis should be obtained, and the causative agent should be identified after managing the anaphylactic emergency.

AUTHOR NOTE

Written consent was obtained from all patients to publish patient information related to this contribution. There are no organizations with conflicts of interest that should be declared in relation to this contribution.

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CE questions must be completed within 3 months and prior to the next issue.

1) Cutaneous involvement (i.e., signs and symptoms) is not obligatory for diagnosing anaphylaxis.

   a. True
   b. False

2) Which of the following is the drug of choice for the initial treatment of anaphylaxis?

   a. Albuterol
   b. Diphenhydramine
   c. Epinephrine
   d. Prednisone

3) Which of the following sites is most ideal for administering intramuscular (IM) epinephrine?

   a. Masseter muscle
   b. Pectoral muscle
   c. Rectus abdominis muscle
   d. Vastus lateralis muscle

4) Which of the following is necessary for obtaining a definitive diagnosis of anaphylaxis?

   a. Aspartate aminotransferase
   b. Platelet count
   c. Tryptase level
   d. White blood cell count