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ANATHYLAXIS, CAUSED BY ANESTHETIC, IN THE DENTAL PRACTICE: PATHOPHYSIOLOGY, CLINICAL MANIFESTATION

O. V. Denefil, O. O. Kulianda, M. O. Levkiv, S. I. Boitsaniuk, N. O. Tverdokhlib

I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

Anaphylaxis is an acute, potentially life-threatening allergic reaction that requires immediate medical intervention. Although rare in dental practice, it can be triggered by local anesthetics, latex, or certain medications used during treatment. Dental professionals must be well-versed in recognizing the signs and symptoms of anaphylaxis to respond promptly and appropriately. A thorough medical and allergy history is essential to identify patients at risk before initiating any dental procedure. Given the rapid onset and progression of anaphylactic reactions, preparedness and training are crucial in preventing serious outcomes.

***The aim of research** – dentists' acquaintance with the clinical picture of anaphylaxis and formation of an algorithm of actions when it occurs in dental practice, with an emphasis on its pathophysiology, in order to increase doctors' awareness of preventive measures that can minimize the risk of anaphylaxis.*

***Conclusions.** Anaphylaxis in dentistry is uncommon but poses a significant threat to patient safety when it does occur. Successful management depends on prompt recognition, the immediate administration of epinephrine, and access to an emergency medical kit. Conducting detailed patient interviews and identifying potential allergens before treatment are the key preventive measures. Continuous professional development and emergency response training play a vital role in ensuring effective care and safeguarding patient health in dental settings.*

Key words:
anaphylaxis, dental emergency, epinephrine, allergy, dentistry.

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E-mail:
denefil@tdmu.edu.ua

АНАФІЛАКСІЯ, ВИКЛИКАНА АНЕСТЕТИКОМ, У СТОМАТОЛОГІЧНІЙ ПРАКТИЦІ: ПАТОФІЗІОЛОГІЯ, КЛІНІЧНА МАНІФЕСТАЦІЯ

О. В. Денефіль, О. О. Кулянда, М. О. Левків, С. І. Бойцанюк, Н. О. Твердохліб

Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України, м. Тернопіль, Україна

Анафілаксія – це гостра, потенційно летальна алергічна реакція, що потребує негайної медичної допомоги. Під час будь-якого стоматологічного втручання пацієнт піддається впливу різних лікарських засобів різноманітними шляхами та у різному дозуванні. Медичні середники часто стають причиною розвитку небажаних реакцій під час проведення стоматологічного лікування. Серед таких реакцій незначну, але дуже небезпечну частину становлять реакції гіперчутливості негайного типу. У стоматологічній практиці вона виникає рідко, але може бути спричинена місцевими анестетиками, латексом або медикаментами. Знання стоматолога про клінічні прояви та алгоритм надання допомоги є критично важливими для збереження життя пацієнта. Особливо важливо враховувати індивідуальний алергологічний анамнез пацієнта перед початком лікування. Оскільки симптоми анафілаксії можуть швидко прогресувати, стоматологи повинні бути готовими діяти оперативно та максимально ефективно.

Мета роботи – *ознайомлення стоматологів із клінічною картиною анафілаксії та формуванням алгоритму дій при її виникненні в стоматологічній практиці з акцентом на її патофізіології для підвищення обізнаності лікарів про профілактичні заходи, які можуть мінімізувати ризик виникнення анафілаксії.*

Висновки. *Анафілаксія в стоматології – рідкісне, але небезпечне ускладнення, що потребує негайного розпізнавання та лікування. Основними складовими успішного менеджменту є швидка діагностика, наявність аптечки невідкладної допомоги та вміння користуватися адреналіном. Важливо проводити ретельний попередній збір анамнезу для виявлення потенційних алергенів. Постійне навчання та відпрацювання дій при анафілаксії допомагає підвищити безпеку пацієнтів у стоматологічній практиці.*

Ключові слова:
анафілаксія, невідкладна стоматологічна допомога, епінефрин, алергія, стоматологія.

Клінічна та експериментальна патологія 2025. Т.24, №2 (92). С. 75-81.

Introduction

The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been points of controversy, varying among different medical subspecialties in various countries. Anaphylaxis is a severe, potentially life-threatening generalized allergic reaction characterized by rapidly developing symptoms and signs, including skin changes (such as redness and itching), mucosal changes (swelling below the skin surface), swallowing and breathing difficulties (due to swollen mouth, throat or tongue), wheezing, tachypnoea, tachycardia, and hypotension [1]. Drug-induced

anaphylaxis is a well-known, life-threatening, and feared side effect for some drug classes, but emerging drug causes of anaphylaxis and novel mechanisms leading to non-IgE-mediated mast cell activation may contribute [2]. Anaphylaxis's susceptibility (or incidence) varies with age, allergen exposure, and predisposing genetic factors. Symptoms of anaphylaxis may progress rapidly and involve multiple target organ systems, including the integumentary, respiratory, gastrointestinal, and cardiovascular systems [3]. Anaphylaxis is a severe allergic reaction that occurs rapidly, primarily due to the quick release of potent, pharmacologically active substances from mast cells and basophils. This release is typically dependent on the presence of immunoglobulin E (IgE). Among the most common triggers of anaphylaxis, anesthetics are considered the primary cause in adults [4].

The aim of research

To acquaint dentists with the clinical picture of anaphylaxis and to form an algorithm of actions when it occurs in dental practice, with an emphasis on its pathophysiology, in order to increase doctors' awareness of preventive measures that can minimize the risk of anaphylaxis.

Main part

The World Health Organization defines anaphylaxis as «a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.»

The World Allergy Organization has reported a rise in the incidence and prevalence of allergies over the past decade. In 2020, the global incidence was estimated to be between 50 and 112 episodes per 100,000 people, while the lifetime prevalence ranged from 0.3% to 5.1%. Although the mortality rate remains low – ranging from 0.05 to 0.51 per million people per year for drug-induced reactions, 0.03 to 0.32 for food-induced reactions, and 0.09 to 0.13 for venom-induced reactions – the rate of recurrence is significantly high, with estimates between 26.5% and 54.0% over a follow-up period of 1.5 to 25 years [5-7]. Various triggers can cause anaphylaxis, the most common being foods, medications, and stings from insects like bees and wasps. Regardless of the allergen, the signs and symptoms of anaphylaxis remain the same and impact multiple systems. Anaphylaxis is a potentially fatal systemic reaction that may arise as a side effect of dental treatment, oral and intravenous sedation, and general anesthesia [8]. Anaphylactic shock is the final stage of anaphylaxis, occurring when tissue perfusion is inadequate, leading to damage in the affected organs.

History. The phenomenon of anaphylaxis is old and has been described in ancient Greek and Chinese medical literature. The first documented anaphylactic patient might have been pharaoh Menes, who died in 2640 BC from a wasp sting, as hieroglyphs tell (Wadell, 1930) [9, 10]. The phenomenon of anaphylaxis was first described in the modern medical literature in 1902 in a study involving protocols for immunizing dogs with jellyfish toxin. The injection of small amounts of toxin in some animals rather than generating protection precipitated the rapid onset of fatal or near-fatal symptoms. The authors named this response «l'anaphylaxie,» which is derived from the Greek words a- («against») and phylaxis («immunity» or «protection») [8, 10]. Despite significant advancements in allergology and fundamental immunology over the last 20 to 30 years, anaphylaxis continues to be primarily diagnosed based on clinical observations. A notable development in this field is the publication of the World Allergy Organization (WAO) clinical criteria for anaphylaxis, which allows clinicians globally to «speak the same language» and report meaningful data. However, these criteria have faced criticism recently, with calls for further refinement [11-13].

Anaphylaxis pathophysiology. Some authors reserve the term anaphylaxis only for IgE-dependent events and the term anaphylactoid to describe IgE-independent reactions that otherwise are clinically indistinguishable. Coombs and Gell first classified 4 types of hypersensitivity (immunopathologic) reactions:

- I, immediate (IgE-dependent);
- II, cytotoxic (IgG, IgM dependent);
- III, immune complexes (IgG, IgM complex dependent);
- IV, delayed (T-lymphocyte dependent).

IgE-dependent reactions can cause anaphylaxis, as can cytotoxic reactions (such as blood transfusion reactions) and immune complex reactions (like gammaglobulin complexes given intramuscularly or intravenously) [14].

The primary molecular mechanism behind anaphylaxis is the classic allergic reaction mediated by immunoglobulin E (IgE), which involves mast cells and basophils [7]. Mast cells are found in all vascularized tissues, while basophils comprise less than 1% of the circulating leukocytes in the blood. Additionally, basophils have only a tiny amount of tryptase compared to the levels expressed by mast cells during allergic reactions. The leading cause of anaphylaxis is a quick immunoglobulin (Ig) E-mediated allergic reaction. IgE levels are also used in diagnosing allergies to identify the specific allergens to which a patient is sensitive [15]. Anaphylaxis is caused by a massive release of biochemical mediators from mast cells and basophils [16].

Mast cell activation primarily occurs when antigens crosslink IgE antibodies bound to FcεRI receptors on the cell membrane. However, other membrane receptors can also activate mast cells or enhance IgE activation. Once activated, mast cells and basophils release mediators that lead to physiological changes, activate other immune pathways, and attract additional immune cells. Preformed mediators, such as histamine, tryptase, heparin, and chymase, are released immediately upon activation (Tabl.1) [15].

Biochemical mediators:

- Histamine increases vascular permeability and vasodilation, leading to tissue hypoperfusion. The body responds to these changes by increasing heart rate and cardiac contraction.
- Prostaglandin D functions as a bronchoconstrictor, simultaneously constricting cardiac and pulmonary arteries. It also potentiates peripheral vasodilation, contributing to the hypoperfusion of vital organs.
- Leukotrienes add to bronchoconstriction and vascular permeability and induce airway remodeling.

➢ The platelet activation factor also acts as a bronchoconstrictor and increases vascular permeability.

➢ TNF-alpha activates neutrophils (as part of stress response leukocytosis) and increases chemokine synthesis [4].. *Anaphylaxis in the dental practice*

A variety of drugs and materials that can cause anaphylaxis are used in dental office (Tabl. 1) [8]. Anaphylaxis in dental offices is caused mainly by drugs and latex-containing products used during dental treatment.

Table 1

Typical causative agents of anaphylaxis in dental practice

Drugs and Materials That May Cause Anaphylaxis During Dental Treatment		
Drugs	Dental materials	Items with latex
Antibiotics; Analgesics; Antiseptics; Local anesthetics	Used in endodontics; Used in impressions.	Gloves, bite blocks, prophy polishing cups, dental rubber dams, orthodontic elastics, adhesive tape, anesthetic cartridges, bite wing tabs, impression materials containing latex, masks, gutta percha.

Allergy to local anesthetics. It is not unusual for patients to claim they are allergic to local anesthetics. Upon careful questioning, however, one generally finds that what they experienced was either a syncopal episode associated with the injection or cardiac palpitations attributed to epinephrine either contained in the solution or released endogenously [17].

There are two groups of local anesthetics (LA) with different chemical characteristics as well as different sensitization power:

➢ benzoic acid ester: benzocaine, clorprocaine, cocaine, piperocaine, procaine, propoxicaine, tetracaine;

➢ amides: lidocaine, bupivacaine, ropivacaine (Fig. 1).

The classification is based on the chemical structure of the intermediate chain. This structural difference affects the pathway by which local anesthetics are metabolize. Esters they are usually metabolized more quickly by the body. Amides they tend to have longer-lasting effects compared to esters.

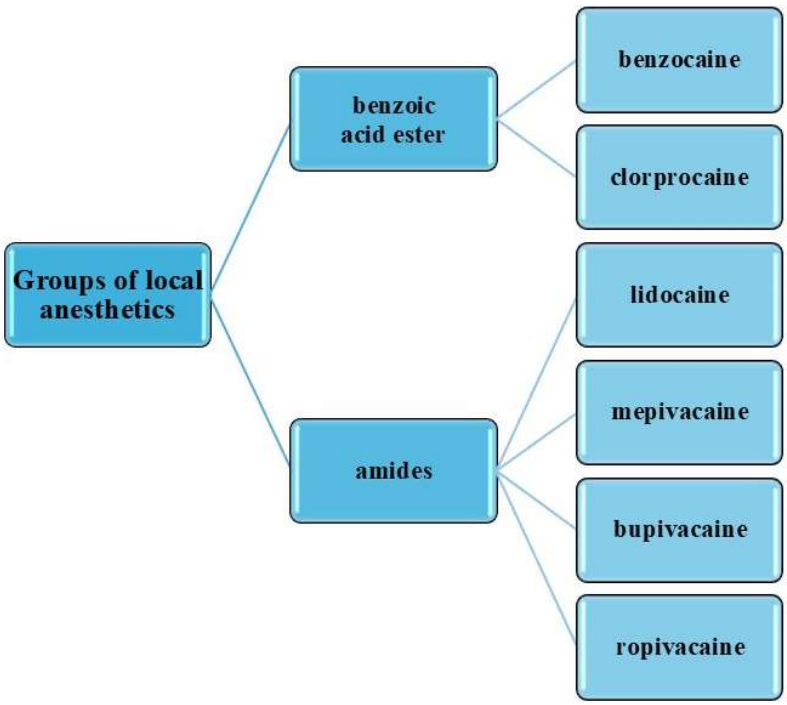

Fig. 1. Classification of local anesthetics drugs

Local anesthetic agents are amphipathic molecules. They bind primarily to sodium channels, potassium and calcium channels, and G-protein-coupled receptors. Local anesthetic agents suppress action potentials in excitable tissues by blocking voltage-gated Na+ channels. In doing so, they inhibit action potentials in nociceptive fibers and block the transmission of pain impulses [18].

These agents are weak bases, tertiary amines with three structures in common:

➢ aromatic group – confers lipid solubility and allows nerve membrane penetration;

➢ intermediate chain – differentiates anesthetic as ester or amide;

➢ amino group – contributes water solubility, which prevents precipitation of anesthetic (Fig. 2).

All local anesthetics consist of 3 principal components, each contributing a distinct property [17]. The vehicle used in local anesthetics is sterile water combined with sodium chloride, which helps maintain the osmotic balance between the anesthetic solution and body tissues. To adjust the pH and minimize the oxidation of vasoconstrictors, buffers such as sodium hydroxide and hydrochloric acid are included. The most commonly used antioxidant in anesthetics is sodium metabisulfite, which helps to prevent the oxidation of the vasoconstrictor. However, adding vasoconstrictor and sodium metabisulfite lowers the pH of the local anesthetic solution, leading to a slower onset of action.

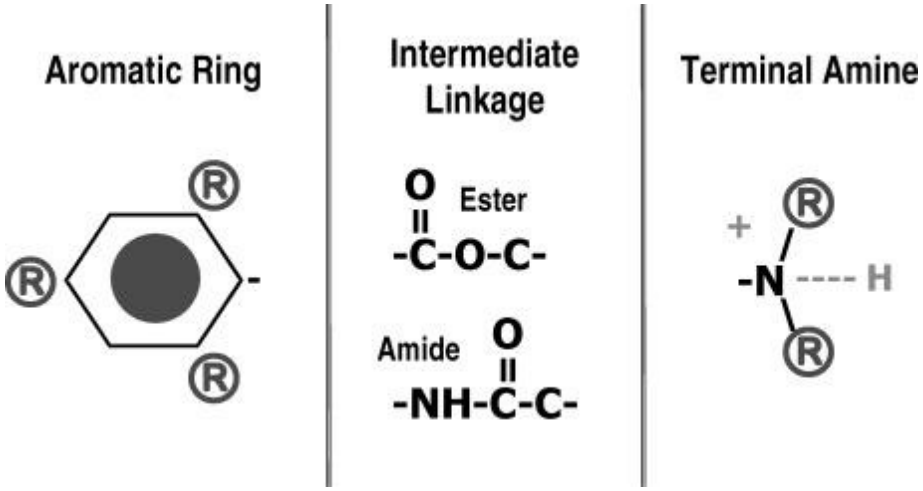

Fig. 2. Local anesthetic structure

Components of a local anesthetic:

- Anesthetic agent
- Vehicle
- Buffers
- Antioxidants
- Vasoconstrictor [19].

Mechanism of action of local anesthetics. Local anesthetic molecules that are lipophilic and uncharged can cross the phospholipid neuronal membrane. The ionized form of these anesthetics binds to open voltage-gated sodium (Na+) channels in a reversible and concentration-dependent way. When the local anesthetic binds, it stabilizes the receptor's inactivated state, preventing further neuronal transmission. The effectiveness of the local anesthetic nerve block depends on its concentration. [18].

Metabolism and Excretion of a local anesthetic. Amide anesthetics are metabolized by liver enzymes and excreted through the kidneys. Individuals with compromised liver blood flow – such as alcoholics, those with liver disease, or those suffering from congestive heart failure (CHF) – and those with renal disease may have lower thresholds for toxicity. Therefore, dosages and the frequency of injections may need to be adjusted accordingly. Ester local anesthetics (LAs) are hydrolyzed in plasma by pseudocholinesterase. The rate of hydrolysis affects their potential toxicity: Chloroprocaine is the least harmful, while Tetracaine is the most toxic. Allergic reactions to ester drugs are typically due to PABA, the primary metabolite of ester anesthetics. In terms of excretion, these anesthetics are mainly eliminated by the kidneys. A percentage of a given dose of an ester local anesthetic will be excreted unchanged in the urine, usually in small concentrations. In contrast, amides are primarily found in urine as the parent compound [20]. Many LA-induced allergic reactions are due to other constituents in the injection solution rather than to the drug itself. Excipients such as preservatives (for example, benzoates used in multi-dose vials) and antioxidants (for instance, metabisulphites used in LA solutions containing adrenaline) can cause allergic reactions. [1, 21].

Clinical features and diagnosis. Anaphylaxis is characterized by quick onset and rapid deterioration. Recognize anaphylaxis based on the ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach:

– Airway and/or Breathing and/or Circulation problems.

– Skin and/or mucosal changes (flushing, urticaria, angioedema) may be absent in up to 20% of cases (e.g., some patients initially present with only bronchospasm or hypotension).

Patients can have an A, B, or C problem or combination (Tabl. 2) [22, 23].

Table 2

ABC approach to recognize it and treat early

Airway problems	Breathing problems:	Circulation problems:
✓ Airway swelling (throat and tongue swelling causing difficulty in breathing/ swallowing; patients may feel their throat is closing). ✓ Hoarse voice. ✓ Stridor (a high-pitched inspiratory noise caused by upper airway obstruction).	✓ Increased work of breathing. ✓ Bronchospasm (wheeze) and/or persistent cough. ✓ Patient becoming tired with the effort of breathing (fatigue). ✓ Hypoxaemia (SpO2<94%) which may cause confusion and/or central cyanosis. ✓ Respiratory arrest.	Signs of shock: ✓ Pale, clammy; ✓ Significant tachycardia (increased heart rate); ✓ Hypotension (low blood pressure). ✓ Dizziness, decrease conscious level or loss of consciousness. ✓ Arrhythmia. ✓ Cardiac arrest.

Treatment. In cases of suspected anaphylaxis, the dentist should immediately stop the procedure, ensure the airway is clear of any materials, and eliminate any contact with the alleged triggering agent from the patient. Adrenaline is the first-line treatment for anaphylaxis. Administer intramuscular (IM) adrenaline early in the anterolateral thigh to address airway, breathing, or circulation problems. A single dose of IM adrenaline is generally well-tolerated and carries minimal risk for individuals experiencing an allergic reaction. If you are uncertain, it's better to give IM adrenaline. If airway, breathing, or circulation problems persist after 5 minutes, repeat the IM adrenaline dose. Intravenous (IV) adrenaline should only be used in specific specialist settings and by those who are trained and experienced in its administration. IV adrenaline infusions are essential for treating refractory anaphylaxis. [22, 23].

The role of antihistamines in anaphylaxis is a topic of debate, but there is a consensus among all guidelines that they should not be considered a first-line treatment. While antihistamines are not recommended for the initial management of anaphylaxis, they can be useful for treating skin symptoms, such as urticaria or angioedema, that may occur after the initial life-threatening symptoms (Airway, Breathing, Circulation) have been addressed. Non-sedating antihistamines, like cetirizine, are preferred in these situations. Additionally, the updated RCUK guidelines advise against the use of corticosteroids for treating anaphylaxis. Similar to antihistamines, corticosteroids are often administered more frequently than adrenaline, which raises concerns about their potential to distract from the timely use of adrenaline during anaphylactic reactions [24-27].

Conclusions

Over the past 30 years, our understanding of anaphylactoid reactions during anesthesia has significantly improved; however, these reactions still pose a significant concern and continue to be debated among dentists. The incidence of anaphylaxis has risen in recent years, highlighting the need for ongoing education on diagnosis and management. Every healthcare professional must be equipped to handle such emergencies.

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Information about the authors:

Denefil O. V. – Prof., DSc, PhD, MD Head of the Departmen of Pathophysiology, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.

E-mail: denefil@tdmu.edu.ua,

ORCID ID: https://orcid.org/0000-0002-3606-5215.

Kulianda O. O. – PhD, Associate Professor, Department of Pathophysiology, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.

E-mail: kulyanda_olol@tdmu.edu.ua,

ORCID ID: https://orcid.org/0009-0008-2096-4890

Levkiv M. O. – PhD, Associate Professor, Department of Dental Therapy, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.
E-mail: levkiv@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0001-7327-051X.
Boitsaniuk S. I. – PhD, Associate Professor, Department of Dental Therapy, Dean of the Faculty of Dentistry, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.
E-mail: boucanuk@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0001-7742-1346.
Tverdokhlib N. O. – PhD, Associate Professor, Department of Dental Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.
E-mail: tverdohlibno@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0002-1247-2430

Відомості про авторів:

Денефіль О. В. – доктор медичних наук, професор, завідувач кафедри патологічної фізіології, Тернопільський національний медичний університет імені І. Я. Горбачевського, м. Тернопіль, Україна.
E-mail: denefil@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0002-3606-5215.
Кулянда О. О. – кандидат медичних наук, доцент кафедри патологічної фізіології, Тернопільський національний медичний університет імені І. Я. Горбачевського, м. Тернопіль, Україна.
E-mail: kulyanda_olol@tdmu.edu.ua,
ORCID ID: https://orcid.org/0009-0008-2096-4890
Левків М. О. – кандидат медичних наук, доцент кафедри терапевтичної стоматології, Тернопільський національний медичний університет імені І. Я. Горбачевського, м. Тернопіль, Україна.
E-mail: levkiv@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0001-7327-051X.
Бойцанюк С. І. – кандидат медичних наук, доцент кафедри терапевтичної стоматології, декан стоматологічного факультету, Тернопільський національний медичний університет імені І. Я. Горбачевського, м. Тернопіль, Україна.
E-mail: boucanuk@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0001-7742-1346.
Твердохліб Н. О. – кандидат медичних наук, доцент кафедри хірургічної стоматології, Тернопільський національний медичний університет імені І. Я. Горбачевського, м. Тернопіль, Україна.
E-mail: tverdohlibno@tdmu.edu.ua,
ORCID ID: https://orcid.org/0000-0002-1247-2430

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