Anaphylaxis to Local Anaesthetics

Iurie Acalovschi
Universitatea de Medicină si Farmacie
"Iuliu Haţieganu" Cluj-Napoca

CEEA Tg. Mures, 2016

Terminology

- Allergy
- Hypersensitivity
- Acute (immediate) Type I
- Delayed (non-immediate) Type IV
- Local
- Systemic
- Anaphylactoid
- Anaphylactic

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 199–211 doi:10.1111/j.1365-2044.2008.05733.x

GUIDELINES

Suspected Anaphylactic Reactions Associated with Anaesthesia

Association of Anaesthetists of Great Britain and Ireland

Membership of the Working Party: N J N Harper, Chairman; T Dixon; P Dugué; D M Edgar; A Fay; H C Gooi; R Herriot; P Hopkins; J M Hunter; R Mirakian; R S H Pumphrey; S L Seneviratne; A F Walls; P Williams; J A Wildsmith; P Wood. Ex Officio: A S Nasser[1], R K Powell[1], R Mirakhur[2], J Soar[3], Executive Officers, AAGBI

[1]British Society for Allergy and Clinical Immunology
[2]Royal College of Anaesthetists
[3]Resuscitation Council UK

The underlying mechanisms

- Mast cells and basophil degranulation
- Release of mediators: histamine, tryptase, leukotriens, prostaglandins, PAF
- Allergic anaphylaxis - immunologic mediated
  - IgE, IgG; previous antigen exposure
  - Immune complex or T-cell dependent (non-IgE IgG)
- Non-allergic anaphylaxis
  - No immune trigger
  - Direct drug action
  - No previous exposure

Clinical manifestations

Organ system	Signs and symptoms
Cardiovascular	Hypotension, tachycardia, arrhythmias, colaps, cardiac arrest
Pulmonary	Cough, dyspnea, bronchospasm, difficulty to inflate
Cutaneous	Generalized erythema, urticaria, angioedema

Anaesthesia-related anaphylaxis

- Incidence
  - Australia 1/10,000-1/20,000 anaesthestics *(Fisher MN, Baldo BA 1993)*
  - France 1/318 anaesthestics *(Laxenaire MC 2001)*
  - Great Britain 1/1,000 anaesthetics, 500 severe reactions each year *(Harper NJN et al, 2009)*
- Mortality
  - 3-9% *(Light KP et al, 2006)*

Table 6. Clinical Features of Anaphylactic and Anaphylactoid Reactions during Anesthesia in France between January 1, 1999, and December 31, 2000

	Anaphylaxis (n = 518)		Anaphylactoid Reactions (n = 271)	
Clinical Symptoms	Patients No. (%)	Sole Feature	Patients, No. (%)	Sole Feature
Cardiovascular symptom	387 (74.7)		92 (33.9)	
Arterial hypotension	90 (17.3)	2	50 (18.4)	1
Cardiovascular collapse	264 (50.8)	32	30 (11.1)	2
Bradycardia	7 (1.3)	0	2 (0.7)	0
Cardiac arrest	31 (5.9)	10	—	0
Bronchospasm	207 (39.8)	7	52 (19.2)	2
Cutaneous symptoms	374 (71.9)	50	254 (93.7)	136
Angioedema	64 (12.3)	—	21 (7.7)	—

Mertens PN et al, Anesthesiology 2003

Diagnostic approach

- History
  - Identification of particular underlining conditions (atopy, asthma, known drugs and food allergies)
  - Information on a previous anaphylactic reaction
    - A detailed description of clinical symptoms
    - Time elapsed between administration and onset of symptoms (immediate vs delayed anaphylaxis)
- Diagnostic tests
  - Histamine and tryptase; detection of specific IgE (sIgE); BAT; skin tests; provocative tests.

Blood tests histamine and tryptase

- Histamine
  - Has a greater sensitivity
  - Allows diagnosis of all types of anaphylaxis
  - Less used (T/2 20 min)
- Tryptase
  - Marker for mast cells and basophil activation
  - T/2 120 min.
  - Diagnostic value at > 25 ng/L
  - The measurement of basal tryptase (<1.5 ng/L) is recommended
  - Normal tryptase levels do not rule out anaphylaxis

Berroa F et al, 2014

Quantification of drug-specific IgE (sIgE)

- Drug coupled with solid phase incubated with patient's serum
- Detection of the bound sIgE with a secondary anti-human IgE antibody, radioisotope (RAST) or fluorescence labelled (FEIA)
- ImmunoCAP (Phodia A) to detect sIgE for succinilcholine

Basophil activation test (BAT)

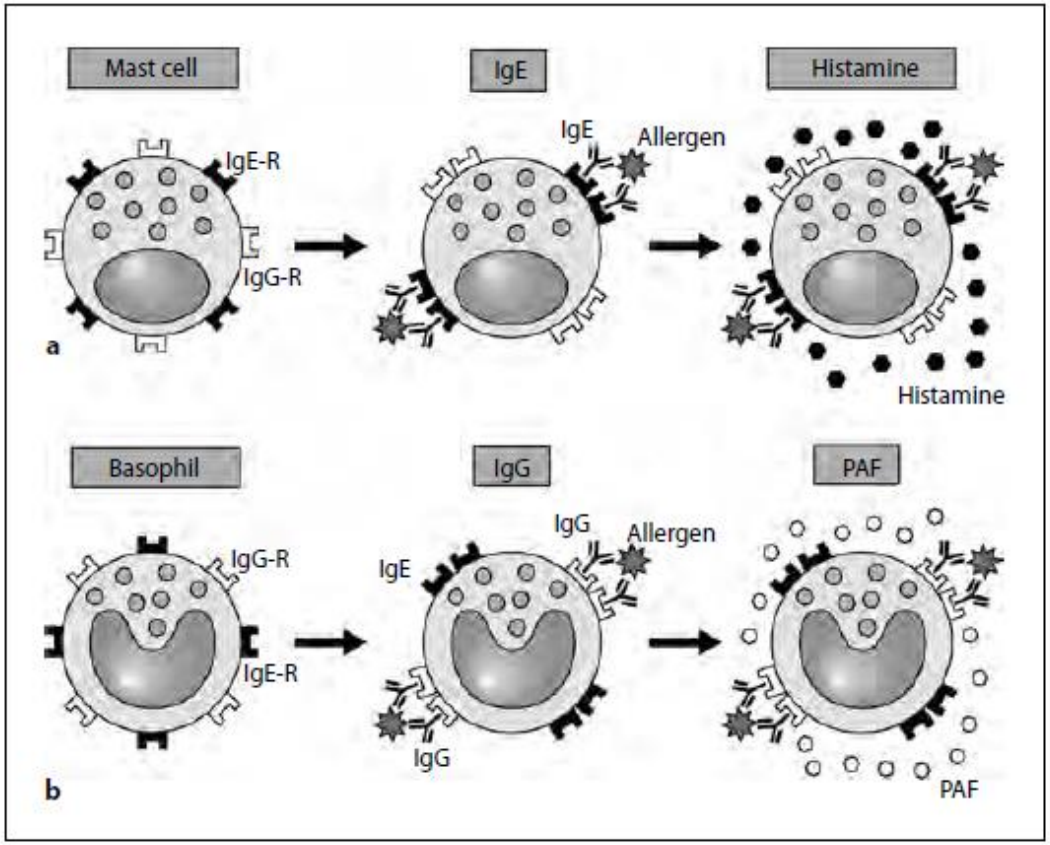

Fig. 1. Two distinct pathways of systemic anaphylaxis: (**a**) in the classical pathway, mast cells, IgE and histamine play important roles, and by contrast (**b**) in the alternative pathway, basophils, IgG and PAF play the major roles.

Karasuyama H et al, 2010

Investigation of basophil activation

- Measurement of released mediators (histamine, leukotriens, PAF)
- Identification of basophil expression markers: expression on basophil membrane of new molecules (CD63, CD203C) as markers of activation
- The basophils are identified with monoclonal antibodies marked with fluorochrome

Skin tests

Performed 4-6 weeks after the reaction and with antihistaminic drugs stopped

- Prick test (undiluted drug)
  - Read after 15 min
  - Considered positive with a wheel of > 3mm than the negative control
- Intradermal test (diluted drug)
  - Read after 15 min
  - A wheel > 8 mm is considered positive
  - Could be painful

Provocative test

- A graded exposure to suspected drug from small to clinically relevant quantities, administered orally, s.c. or i.v.
- Carries a risk of anaphylaxis
- Should be conducted under strict supervision
- Requires patient's written consent

Anaphylaxis to local anaesthetics

Local anaesthetics are used in dentistry, ophtalmology, minor surgery, endoscopy, obstetrics, dermatology

Table 2. Local anaesthetics (LA)

Amide group	Esther group
Lidocaine	Benzocaine
Prolocaine	Procaine
Mepivacaine	Chloroprocaine
Bupivacaine	Tetracaine
Levobupivacaine	
Ropivacaine	
Articaine	

Incidence

Rare, 0.1-1%

Table 2. Drugs and related compounds involved in perioperative anaphylaxis (not exhaustive)

Substance	%*	Examples
NMBA	58.2	Succinylcholine *Benzylisoquinolines*: atracurium, cisatracurium, doxacurium, mivacurium *Aminosteroids*: pancuronium, rapacuronium, rocuronium, vecuronium
NRL	16.7	Gloves, tourniquets, catheters
Antibiotics	15.1	β-lactams (penicillins, cephalosporins), vancomycin, quinolones *Cave*: locally applied antibiotics
Colloids	4	Gelatine, hydroxyethyl starch, dextrans, albumins
Hypnotics	3.4	Barbiturates: thiopental, methohexital Nonbarbiturates: propofol, midazolam, etomidate, ketamine
Opioids	1.3	Phenanthrenes: morphine, codeine Phenylpiperedines: alfentanyl, fentanyl, remifentanyl, sufentanyl and meperidine
Miscellaneous	1.3	Antiseptics: chlorhexidine, povidone iodine Iodinated radiological contrast and dyes (patent and isosulphan blue) Local anaesthetics: benzoic acid esters and amides Aspirin, NSAID and paracetamol (acetaminophen) Ethylene oxide Protamine and heparins

NMBA, neuromuscular blocking agent; NRL, natural rubber latex; NSAID, nonsteroidal anti-inflammatory drugs.
*According to (14, 49).

Ebo DG et al, Allergy 2007

Local hypersensitivity reactions

- Clinical expression: allergic contact dermatitis
- Delayed type response (72 hours)
- Immune cell mediated (T-cell, non-IgE)
- Common with use of esther compounds, also possible with amide derivatives

Lidocaine Contact Allergy Is Becoming More Prevalent

Derek To, BSc,* Irèn Kossintseva, MD, FRCPC, FAAD,† and
Gillian de Gannes, MD, FRCPC, FAAD*†‡

BACKGROUND Allergic contact dermatitis (ACD) to lidocaine is rising in prevalence. This is due to a growing number of over-the-counter (OTC) products containing topical amide and ester anesthetics. The phenomenon poses a real threat to the authors' surgical anesthetic options.

OBJECTIVE To investigate the epidemiology of topical anesthetic ACD in British Columbia, Canada and provide an approach for clinicians to deal with this problem.

MATERIALS AND METHODS A retrospective chart review of 1,819 patients who underwent patch testing at the University of British Columbia Contact Dermatitis Clinic between January 2009 and June 2013 was completed. The authors also performed a detailed review of Canadian OTC preparations containing lidocaine in 2013.

RESULTS The prevalence of ACD to local anesthetics is significant at 2.4%. The most common allergen is benzocaine (45%) followed by lidocaine (32%) and dibucaine (23%).

CONCLUSION The proportion of ACD caused by lidocaine is higher than expected. This is likely secondary to an increase in OTC medicaments containing lidocaine. Patients who are patch test–positive to a local anesthetic should be challenged intradermally to confirm clinical relevance. Because ACD is a delayed Type IV hypersensitivity reaction (localized dermatitis), the risk of anaphylaxis is not a concern.

Systemic anaphylaxis to LA

- Immediate type I and delayed type IV reactions
- Immune mediated: IgE and T-cell dependent
- Clinical manifestation: from low-grade to sever (anaphylactic shock)
- Adverse reactions with clinical manifestations similar to anaphylaxis

Adverse reactions that mimic alnaphylaxis to LA

- 1. Psychologic responses: anxiety, panic attack, spasmofilia crisis (lipotimia, sensation of heat, paresthesia, rush, polypnea, hyperventilation, chest tightness), vaso-vagal syncope (pallor, bradycardia)
- 2. Intravascular administration of LA and systemic toxicity (cardiovascular, CNS)
- 3. Intravascular absorption of adrenaline (tachycardia, arrhythmias)
- 4. Hypersensitivity to additives (sulfites, paraben)
- 5. Hypersensitivity to latex (cartriges containing LA and latex cups and gloves)
- 6. True IgE mediated LA anaphylaxis

British Journal of Anaesthesia **108** (6): 903–11 (2012)
doi:10.1093/bja/aes162

BJA

IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective

M. V. Bhole[1], A. L. Manson[2], S. L. Seneviratne[2] and S. A. Misbah[1*]

[1] Department of Immunology, Oxford University Hospitals NHS Trust, Academic Street, Level 4, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

[2] Department of Clinical Immunology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

* Corresponding author. E-mail: siraj.misbah@ouh.nhs.uk

- 1951-2011: 2976 patients suspected for IgE-mediated allergy
- 29 confirmed (0.97%)
- 22/29 of cases (75%) documented to an amide agent

Diagnostic strategy

- History
  - Detailed description of the event's symptoms: Quincke's edema, bronchospasm, hypotension, anaphylactic shock
- Tryptase measurement
  - An increase in blood concentration 30-60 min after anaphylactic episode
  - A second measurement is recommended for baseline values
- sIgE measurement
  - No value for LA. The IgE antiprocaine and antilidocaine were never positive

Gullen C et al, 2012

Skin tests (LA which do not contain adrenaline or additives)

- Prick test
  - Non-diluted LA solutions
  - The results usually negative
- Intradermal test
  - Performed only after negative prick test
  - LA dilution 1/10
  - Painful procedure
  - To be increased gradually: 1/1000, 1/100, 1/10
  - May be useful in detection of delayed reactions
  - High rate of false positive results
- Patch test: diagnosis of contact allergies

Provocative tests

- The ‘gold standard’ to establish or exclude the diagnosis of hypersensitivity to LA
- Represents the last stage of diagnosis in case of the absence of reliable skin tests
- Should start with a low dose, but a maximum single dose must be achieved
- Dosage and time intervals: 0.1, 0.5, 1.0, 2.0 mL of undiluted LA (without adrenaline) at 30 min interval
- Lack of hypersensitive reaction within 30 min is considered negative result
- In anxious patients or complaints during placebo administration, a reverse provocative test may be used

Table 1. Reverse placebo provocation test [2, 26]

Procedure	Information given to patient	Result of provocation	Recommended proceeding
LA injection	LA injection	Patient reports complaints	Continuation of procedure
Saline injection	Next dose of LA injection	Patient reports complaints	Continuation of procedure
LA injection	Placebo injection	Patient does not report complaints	Continuation of procedure
		Patient reports complaints	Positive result of provocation test
LA injection	Informing the patient about previous procedures; LA injection afterwards	Patient does not report complaints	Negative result of provocation test

Brockow K et al, Allergo J Int 2015

Practical aspects: the pregnant woman

- Suspected for LA hypersensitivity
- Presented late to the obstetrician
- The provocative test is performed in the delivery room before insertion of the epidural catheter
- The skin test (i.d.) is performed:
  - when skin tests are negative: provocative test with the suspected undiluted LA (without adrenaline)
  - when skin test is positive: provocative test with alternative undiluted LA (without adrenaline and preservative-free)
  - when skin tests cannot be performed: provocative test with alternative LA, not skin tested

Treatment of severe anaphylaxis

- Initiate CPR and call for help
- Secure airway and control ventilation
- Administer 1 mg bolus of adrenaline every 10 min (1-2 min)
- Replenish vascular space with crystalloid solutions up to 30 ml / kg, then replace with colloids
- For patients with sympathectomy:
  - adrenaline dose must be increased
  - if unresponsive, consider glucagon (1-2 mg i.v. every 5 min), noradreanline (0.1 mg/kg/min), or vasopressin (40 U)
- Treat bronchospasm
- Hydrocortisone hemissuccinate 200 mg i.v. every 6 h

Thank you !