



Anaphylactic reactions to local anesthetics in dental practice: a nationwide French retrospective study

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Abstract

Objectives The primary aims of the present study were (1) to quantify and characterize anaphylactic type I reactions related to local anesthetics (LAs) drawing on the French Pharmacovigilance Database System over a 35-year period and (2) to focus on reactions associated with dental procedures. The secondary aim was to infer an incidence rate in dental practice.

Materials and methods All cases of anaphylactic reactions were selected using the algorithmic Standardized MeDRA Query “anaphylactic reaction.” For each reaction, comprehensive data were collected, in particular the severity of symptoms, risk factors for anaphylaxis, and allergy testing. Imputability was assessed and a crude incidence rate in dental practice was estimated.

Results The first-line search identified 416 anaphylactic reactions, mostly of grade II (138) or III (240) severity. When restricted to dental practice, this number fell to 26 (grade I: 4; grade II: 10; grade III: 11; and grade IV: 1). Lidocaine was most often involved (81.49%) and mostly associated with anaphylactic reactions of grade II and III. Overall, 11 cases of fatal anaphylaxis were recorded, but no in dental practice. In dental practice, lidocaine was also the most frequently involved LA (57.69%).

Conclusions All these findings highlight the very low incidence of type I-IgE-mediated reactions to LA, particularly in dental practice. The incidence rate of LA anaphylactic episodes in dental practice was estimated as 0.0261 anaphylactic episodes per million LA cartridges.

Clinical relevance True anaphylactic reactions to LAs do occur and may justify a thorough investigation in dental practice.

Keywords Anaphylaxis · Local anesthetics · Dental care · Survey

Introduction

Local anesthetics (LAs) are widely used in local or regional anesthesia techniques. In particular, LAs are the most commonly administered drugs in dental practice and most of their side effects are well known [1]. It has been estimated

that daily, approximately 6 million people around the world are subjected to their effects in dentistry [2]. LAs have three components, a lipophilic (aromatic) group, an intermediate chain linkage, and a hydrophilic (amine) group. Based on their chemical structure, LAs are classified as ester or amide compounds. LAs irreversibly block impulse conduction along nerve axons. The combination of small molecule size and aromatic ring structure allow LAs to rapidly interact with the cells' voltage-gated sodium channels and inhibit their function [3]. Usually, LA use is effective and uneventful. The overwhelming majority of the time, an adverse reaction to LAs is not truly allergic in nature. Occasionally, patients suffer systemic adverse reactions (ADRs) after LA administration. These may range from minor transient vasovagal attacks to life-threatening anaphylaxis [4].

However, true allergic reactions to LAs may rarely occur and have been estimated to be less than 1% of all reactions occurring after administration of LAs [5–9]. Gall et al.

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investigated 43 patients with a history of ADR to LA over a 10-year period using first-line skin prick test (SPT) and intradermal test (IDT), specific IgE tests, and challenge tests [6]. All the results of the first-line tests were negative and only three patients reacted after a subcutaneous challenge with the causative LA. Rood completed skin and intraoral challenges for 44 adult patients suspected of having a LA allergy in dental practice and concluded that a confirmed allergy was not present in any of the cases, but the reactions were instead of a psychogenic origin [7]. In 199 patients suffering from alleged lidocaine hypersensitivity, Amsler et al. demonstrated that true lidocaine hypersensitivity occurred in only one patient [8]. In addition, Bhole et al. revised the literature from 1975 to 2011 and identified 29 out of 2978 patients with an IgE-mediated allergy to LA (mainly amide agents), representing a prevalence of 0.97% using SPT or IDT and/or subcutaneous challenge [9].

When present, the causative mechanism of an allergic reaction to LA is most often a delayed-type hypersensitivity reaction, i.e., a type IV reaction via skin contact, but seldomly there may be an immediate-type reaction, i.e., a type I anaphylactic reaction after LA injection [10, 11]. Type I hypersensitivity to LA has been confirmed by demonstrating specific IgE antibodies against the drug and positive subcutaneous challenges in some case reports or series [6, 9, 12].

We performed this study because in dentistry, evidence of such specific mechanism is very rarely fully documented, mostly because of the lack of appropriate immunological investigations [6, 13]. This makes it difficult to report accurately on the true incidence of this potentially life-threatening incident. To our knowledge, only one Australian survey estimated the incidence of anaphylaxis to be 1 in 22 million LA injections, i.e., 0.0454 anaphylactic episodes per million LA cartridges in dental practice [4]. But this estimation was based mainly on clinical symptoms and not on immunological investigations.

The main aims of this study were (1) to quantify and characterize anaphylactic type I reactions related to LAs drawing on the French Pharmacovigilance Database System (FPDS) and (2) to focus on reactions associated with dental procedures, over a 35-year period. The secondary aim was to infer a crude incidence rate of such reactions in dental practice based on appropriate immunological tests.

Material and methods

Study design

The FPDS has recorded all adverse drug reactions (ADRs) reported spontaneously by healthcare professionals since 1985, and also by patients themselves or by patient associations since 2011, which are collected by the 31 French

regional pharmacovigilance centers [14]. This reporting is entirely voluntary. Every ADR report is analyzed by pharmacologists in the regional pharmacovigilance center. ADRs are then registered in the FPDS and encoded according to the Medical Dictionary for Regulatory Activities (MedRA) classification [15].

Data collection

First, we collected all cases of anaphylactic reactions to LAs available in France: procaine, lidocaine, prilocaine, articaine, mepivacaine, bupivacaine, and ropivacaine as recorded in the FPDS from September 1985 to April 2020. Cases of anaphylaxis were selected using the algorithmic Standardized MedDRA Query (SMQ) with the term “anaphylactic reaction.” SMQ are groupings of MedDRA terms that represent a defined medical condition or area of interest. They are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. Terms included in SMQ relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory data, etc. [16, 17].

In this study, the inclusion criteria were established by applying those from the Second Symposium on the Definition and Management of Anaphylaxis [18]. According to this definition, anaphylaxis is a serious systemic reaction fulfilling at least one of the three following clinical criteria:

- Acute onset of an illness (within minutes to several hours) with involvement of the skin, mucosal tissue, or both and respiratory compromise, or reduced blood pressure, or associated symptoms of end-organ dysfunction;
- Occurrence of two or more of the following signs, which appear rapidly, after exposure to a likely allergen for that patient (within minutes to several hours): involvement of the skin or mucosal tissues, respiratory compromise, reduced blood pressure or associated symptoms, or persistent gastrointestinal symptoms;
- Reduced blood pressure after exposure to a known allergen for that patient (within minutes or several hours): infants and children: low systolic blood pressure (age-specific) or a > 30% drop in systolic blood pressure; adults: systolic blood pressure < 90 mmHg or > 30% decrease from that person's baseline.

All cases that did not match all these criteria were excluded. From this first-line collection, we selected all cases recorded as anaphylactic reaction and, ultimately, the cases occurring for dental procedures.

We classified all these reports according to the Ring and Messmer severity scale of anaphylactic reactions (Table 1) [19].

Imputability was classified into five levels according to the so-called French causality assessment method [20].

Table 1 Severity scale of anaphylactic reaction according to Ring and Messmer [19]

Grade	Symptoms
I	Skin symptoms and/or mild fever reaction
II	Measurable but not life-threatening cardiovascular reaction (tachycardia, hypotension), gastrointestinal disturbance (nausea) or respiratory disturbance
III	Shock, life-threatening spasm of smooth muscles (bronchi, uterus, etc.)
IV	Cardiac and/or respiratory arrest

Briefly, the combination of chronological and semiological scores results in an intrinsic score of imputability corresponding to five levels: I0: not related; I1: doubtful; I2: possible; I3: probable; and I4: almost certain.

Data analysis

For each case, the following data were collected: gender, age, clinical features, severity of symptoms, emergency treatment, possible risk factors for anaphylaxis, any concomitant medications and results of allergy testing, first-line tests: SPT and IDT; second-line tests: specific IgE assay and subcutaneous challenge (when available). Imputability was then evaluated.

Analysis of descriptive statistics was performed using Microsoft Excel 365 (Microsoft Corporation, France). We calculated numbers and percentages for each variable, along with mean $\pm$ standard deviation (SD).

Ethics approval

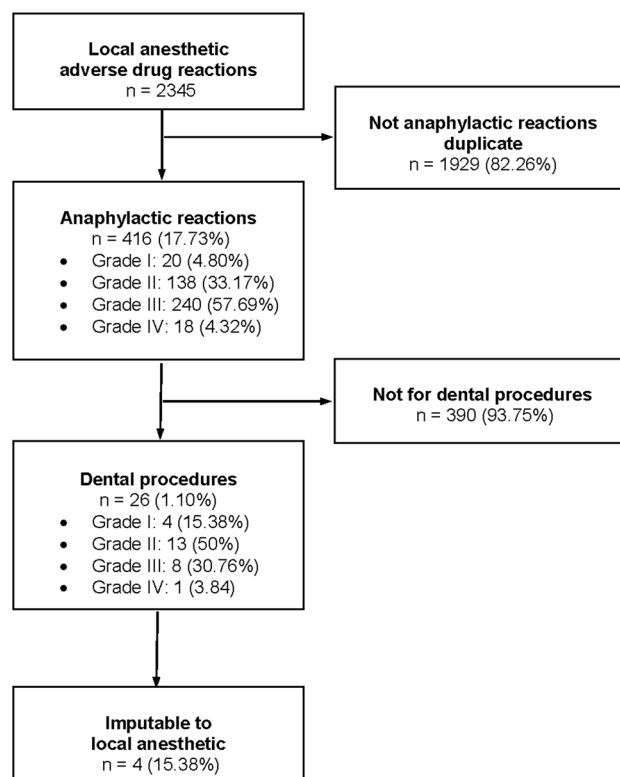
This study was carried out using data from the FDPS, was anonymous, and did not require ethical approval according to French legislation.

Results

Case selection

The first-line search identified a total of 2345 cases of ADRs related to the selected LAs declared to the FPDS. This number fell to 416 when focusing on anaphylactic reactions to these LAs and after removing duplicates. Overall, 20 of these reactions were classified as grade I, 138 as grade II, 240 as grade III, and 18 as grade IV severity. When restricted to dental practice, this number fell to 26 cases (grade I: 4; grade II: 10; grade III: 11 and grade IV: 1) (Fig. 1).

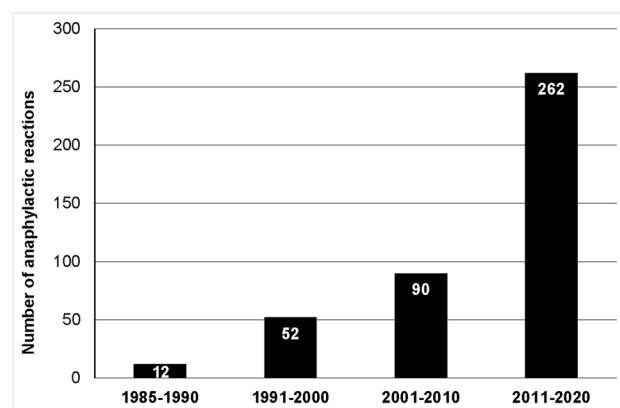
Regarding the dates that these cases were reported, we observed a steady increase during the first three decades

**Fig. 1** Flow chart of case selection

from 1985 to 2010 and a substantial threefold increase during the last decade 2011–2020 (Fig. 2).

Demographics

Patients included 256 (61.53%) women and 160 (38.46%) men, with a sex ratio of 0.63 and a mean age ($\pm$ SD) of 47 ± 13 years (range: 26 days to 89 years). The age distribution highlighted the prevalence of the fourth, fifth, sixth, and seventh decades

**Fig. 2** Number of French Pharmacovigilance Database System reports on anaphylactic reactions involving local anesthetics from 1985 to 2020

for both genders (Table 2). Except for the first decade, women were more widely represented in all the other age groups. Of the patients, 49 (11.77%) were children younger than 18 years.

When restricted to dental practice, there were 19 (73.07%) women and seven (26.92%) men with a sex ratio of 0.37 and a mean age ($\pm$ SD) of 44 ± 7 years (range: 10–78 years). Only three (11.53%) patients were children younger than 18 years (Table 3).

Local anesthetics

Lidocaine was the LA most often involved as cited in 339 reports (81.49%) and mostly associated with anaphylactic reactions of grades II and III severity (Table 4). Mepivacaine,

articaine, and procaine were the other LAs listed in these reports but with a much lower frequency (in 4.80%, 3.12%, and 1.68% of the cases respectively). There were also some rare reports of combinations of lidocaine or mepivacaine with ropivacaine or bupivacaine injected for pain control.

A total of 11 cases of fatal anaphylaxis associated with LAs were recorded in the database during this period, nine associated with lidocaine, one with mepivacaine, and one with the combination lidocaine + ropivacaine.

In dental practice, lidocaine was the LA most often mentioned, listed in 15 of the 26 reports (57.69%), followed by articaine in nine reports (34.61%), and mepivacaine and procaine in one report each (3.84%) (Table 3). No fatal case was reported in dental practice.

Table 2 Gender and age (year) distribution of the patients

Age	< 10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
Female	3	24	20	38	47	53	41	20	10	256
Male	3	19	7	24	29	34	27	11	6	160
Total	6	43	27	62	76	87	68	31	16	416

Table 3 Demographic characteristics and allergy history of the patients in dental practice

Patient gender, age	LA agent	Prior contact with the agent	Associated atopic features	Concomitant drugs
1: F 45	Lidocaine	NA	NA	Bromazepam
2: M 50	Lidocaine	No	NSAID: asthma	No
3: F 55	Lidocaine	Yes: urticaria	NSAID: urticaria	No
4: M 10	Articaine	No	No	No
5: M 53	Articaine	Yes: well tolerated	No	Amoxicillin
6: F 38	Articaine	NA	No	Amoxicillin
7: F 62	Lidocaine	NA	Sulfonamide, ampicillin, iodine: asthma, dermatitis	No
8: F 46	Articaine	NA	NA	No
9: F 39	Lidocaine	Yes: well tolerated	NA	No
10: M 53	Mepivacaine	Yes: Facial edema	NSAID: urticaria	No
11: F 74	Lidocaine	NA	NA	Amoxicillin
12: M 44	Articaine	NA	NA	No
13: F 18	Lidocaine	NA	Neomycin: dermatitis	No
14: M 59	Articaine	NA	NA	No
15: M 13	Articaine	NA	NA	No
16: F 47	Articaine	Yes: well tolerated	No	No
17: F 71	Lidocaine	NA	NA	No
18: F 33	Lidocaine	NA	NA	No
19: F 35	Lidocaine	NA	NA	No
20: F 52	Lidocaine	NA	NA	No
21: F 57	Lidocaine	NA	NA	No
22: F 12	Lidocaine	NA	Mite: dermatitis	No
23: F 30	Procaine	NA	NA	No
24: F 44	Lidocaine	Yes: cardiac arrest	NSAID, penicillin: asthma, edema	Amoxicillin
25: F 27	Lidocaine	Yes: facial edema	Penicillin, cephalosporin: asthma, edema	No
26: F 78	Articaine	NA	NA	Amoxicillin

LA, local anesthetic; F, female; M, male; NA, not available; NSAID, non-steroidal antiinflammatory drugs

Table 4 Local anesthetic agents noted in the anaphylaxis reports and severity of the reactions according to Ring and Messmer [19]

Reports	Procaine	Lidocaine	Mepivacaine	Articaine	Lidocaine Ropivacaine	Lidocaine Bupivacaine	Mepivacaine Ropivacaine	Mepivacaine Bupivacaine
Number	7	339	20	13	16	14	5	2
Severity								
I	0	16	1	1	1	1	0	0
II	3	114	6	4	5	5	1	0
III	4	195	12	8	9	7	3	2
IV	0	14	1	0	1	1	1	0

Clinical features in dental practice

According to the Ring and Messmer severity scale, 4 of these 26 cases of LA anaphylaxis in dental practice were classified as grade I because these patients were only affected by cutaneous symptoms (rash, pruritis, facial edema); 13 as grade II because of cardiovascular symptoms (mainly hypotension) and/or respiratory disturbances (mainly dyspnea) generally associated with cutaneous symptoms; 8 as grade III because patients exhibited shock associated or not associated with angioedema and one as grade IV because a cardiac arrest (but not fatal) was reported (Table 5). All of the patients were admitted to an emergency department but only four of them were directly hospitalized in an intensive care unit. Corticosteroids, mostly intravenously administered prednisolone or methylprednisolone, in combination or not with antihistamines, were used as first-line treatments in the vast majority of the cases and intramuscular epinephrine in the most severe case (Table 5). The outcome of these 26 cases was complete recovery. For six cases, other drugs, mainly amoxicillin (5 cases), were also suspected to be involved in the occurrence of the anaphylactic reaction (Table 3).

Allergy history in dental practice (Table 3)

Comorbidities such as atopic urticaria/dermatitis, edema, and asthma were reported in eight cases, mostly associated with non-steroidal antiinflammatory drugs (NSAIDs) (4 cases) or penicillin (3 cases). No food intolerance was recorded. Interestingly, seven patients reported a history of previous medication with the LA involved in the anaphylactic reaction, three of whom had had good tolerance but one had experienced a cardiac arrest (case 24).

Allergy tests in dental practice (Table 6)

First-line skin tests, SPT or IDT, for suspected LA were available for 14 of 26 patients. SPT results were positive in four cases and IDT results were positive in three cases.

An assay for specific IgE was performed in 4 patients and 2 were positive to the suspected LA, namely lidocaine. In the two patients with negative results on assay for specific IgE, the diagnosis of non-IgE-mediated hypersensitivity reaction was established. A subcutaneous challenge test for the suspected LA was performed for 5 patients and was positive for lidocaine in 3 cases. It is of important to underline that cross-reactivities could be suspected between lidocaine and articaine in case 6, on the basis of positive results for specific IgE tests, and between lidocaine and ropivacaine in case 7, on the basis of positive IDT results. Cross-reactivity between lidocaine and articaine was evidenced in case 13 via subcutaneous challenge to both of these LAs.

Imputability was classified according to the so-called French causality assessment method [20]. In 14 cases, the imputability was classified as possible in the absence of allergic assessment through appropriate tests. In 7 cases, the imputability was doubtful because of the negative results for skin tests or specific IgE assay. In one case, the imputability was classified as probable because of the positive result for specific IgE assay even though the skin test results were negative. In 4 cases, the imputability was assessed as almost certain because of the positive reaction to a challenge test to lidocaine (cases 3, 7, and 13) or because two grade IV anaphylactic reactions to lidocaine injection were recorded in the database even though the skin test results were negative (case 24). It should be noted that in this case 24, assessment with an assay for specific IgE specific or with subcutaneous challenge was not available.

Estimation of a crude incidence rate of anaphylaxis associated with LA in dental practice

The sales of LA dental cartridges in France over the past 10 years have been evaluated by the pharmaceutical industry at 1000 per practitioner per year. In France, the number of dentists has averaged 42,000 for 10 years [21]. This represents a total of 42 million LA cartridges per year used in dental practice in France. Of the 26 cases selected from the

Table 5 Characteristics of allergy in dental practice

Patient	Clinical features	Emergency treatment	Grade of severity [*]
1	Hypotension, dyspnea, syncope	Antihistamine	II
2	Shock, angioedema	Antihistamine	III
3	Pruritis	Antihistamine	I
4	Pruritis	Antihistamine, prednisolone	I
5	Nausea, hypotension, pruritis	Antihistamine, prednisolone	II
6	Shock	Antihistamine, prednisolone	III
7	Shock	NA	III
8	Rash, facial edema	Antihistamine, prednisolone	I
9	Angioedema, urticaria, dyspnea	Antihistamine	II
10	Hypotension, bradycardia, facial edema	NA	II
11	Hypotension, erythema	Methylprednisolone	II
12	Dyspnea, facial edema	Antihistamine, prednisolone	II
13	Dyspnea, urticaria, nausea	Prednisolone	II
14	Hypotension, erythema, pruritis	Antihistamine, prednisolone	II
15	Facial edema	Antihistamine, prednisolone	I
16	Dyspnea, erythema facial edema	Antihistamine, prednisolone	II
17	Shock, angioedema	Methylprednisolone	III
18	Shock	NA	III
19	Shock	NA	III
20	Shock	NA	III
21	Angioedema	NA	II
22	Hypotension, tachycardia	Antihistamine	II
23	Shock	NA	III
24	Cardiac arrest	Epinephrin, prednisolone	IV
25	Dyspnea, facial edema, syncope	Prednisolone	II
26	Rash, erythema, pruritus, hypotension	Antihistamine, prednisolone	II

NA, not available; ^{*} according to Ring and Messmer [19]

FDPS, 11 were recorded during this period. Thus, crude incidence rate of LA anaphylactic episodes in dental practice is estimated at $11/420 \text{ millions} = 0.0261$ anaphylaxis episode per million LA cartridges.

Discussion

This study covering a 35-year period highlighted that anaphylactic reactions to LA are not frequent, representing 17.73% of all ADRs and that true IgE-mediated anaphylaxis to LAs in dental practice is a very rare event, with only four cases out of 2345 (0.17%) LA-related ADRs recorded in the FPDS, and without fatal outcome. This proportion of all ADRs is very close to that reported by Incaudo et al. who reviewed the clinical history of 71 patients with suspected LA allergy and identified 15% of patients with immediate generalized reactions [22].

Due to this rarity and the paucity of reports, it is difficult to estimate a crude incidence rate of true anaphylaxis to LA in dental practice. In an Australian survey, Sambrook

et al. identified 16 cases of anaphylaxis out of a total of 227 suspected ADRs to dental LAs over a 35-year period and estimated the incidence of anaphylaxis to be 1 in 22 million LA injections, i.e., 0.0454 anaphylactic episodes per million LA cartridges [4]. This is approximately twofold higher than the incidence of 0.0261 anaphylactic episodes per million LA cartridges estimated in our study. However, it should be noted that in the Australian survey, the diagnosis of anaphylaxis was mainly based on clinical symptoms and not on immunological investigations as in our study. This could lead to an overestimation of the incidence in the Australian survey.

It is interesting to note the steady increase in the reporting dates throughout the first three decades of the investigation period and the substantial threefold increase in the last decade. This increase may reflect better reporting of anaphylactic reactions to LAs in the FPDS, thus suggesting better efficiency of the drug monitoring program. Another explanation could be improved better information on such reporting to the FPDS in the training of French practitioners.

Table 6 Results of allergy tests in dental practice

Patient	SPT	IDT	IgE	Challenge test	Causality assessment*
1	NA	NA	NA	NA	Possible
2	NA	NA	NA	NA	Possible
3	P: lidocaine	NA	P: lidocaine	P: lidocaine	Almost certain
4	NA	N: lidocaine, articaine	NA	NA	Doubtfull
5	N: lidocaine, articaine, amoxicillin, latex	N: lidocaine, articaine, amoxicillin, latex	NA	NA	Doubtfull
6	N: lidocaine, articaine	N: lidocaine, articaine	P: lidocaine, articaine	NA	Probable
7	N: mepivacaine, articaine	P: lidocaine, ropivacaine	NA	P: lidocaine	Almost certain
8	NA	NA	NA	NA	Possible
9	P: lidocaine	N: lidocaine	N: lidocaine	Lidocaine: well tolerated	Doubtfull
10	P: mepivacaine	P: lidocaine, mepivacaine N: articaine	N: lidocaine, mepivacaine	Lidocaine: well tolerated	Doubtfull
11	N: lidocaine, amoxicillin, latex	N: lidocaine, amoxicillin, latex	NA	NA	Doubtfull
12	NA	NA	NA	NA	Possible
13	P: lidocaine, articaine	P: lidocaine, articaine	NA	P: lidocaine, articaine	Almost certain
14	N: articaine	NA	NA	NA	Possible
15	NA	NA	NA	NA	Possible
16	N: lidocaine, articaine, ropivacaine, bisulfite	N: lidocaine, articaine, ropivacaine, bisulfite	NA	NA	Doubtfull
17	NA	NA	NA	NA	Possible
18	NA	NA	NA	NA	Possible
19	NA	NA	NA	NA	Possible
20	NA	NA	NA	NA	Possible
21	NA	NA	NA	NA	Possible
22	NA	NA	NA	NA	Possible
23	NA	NA	NA	NA	Possible
24	N: lidocaine, amoxicillin, ketoprofen, latex	N: lidocaine, amoxicillin, ketoprofen, latex	NA	NA	Almost certain
25	N: lidocaine, ropivacaine, latex	N: lidocaine, ropivacaine, latex	NA	NA	Doubtfull
26	NA	NA	NA	NA	Possible

SPT, skin prick test; IDT, intradermal test; IgE, specific immunoglobulin E assay; P, positive; N, negative; NA, not available; * according to Begaud et al. [20]

In our work, the LA reactions occurred mostly in middle-aged people, with females being involved in the majority of cases. These results are in accordance with previous studies focusing on allergic reactions after an anesthetic procedure with LAs [23].

Allergic reactions have been primarily reported with procaine, an ester-type LA containing a para-amino-benzoic acid chain in its structure that is highly antigenic, as case 23 of our study [24]. Therefore, procaine is no longer used for dental procedures except for patients with specific hepatic porphyria (and managed in hospital for dental care). Hypersensitivity to the amide-type LA alone is rare but can occur. In our study, lidocaine was the LA most frequently involved in anaphylactic reactions (88.70%), alone or combined with bupivacaine or ropivacaine in few cases. This finding is also

in accordance with previous studies [5, 23], and can probably be attributed to lidocaine being the most widely used LA agent in medical practice [23]. When restricted to dental practice, this proportion decreased to 57.70%, probably highlighting the increased use of other LAs in dental practice, articaine and mepivacaine in particular. Importantly, it should be noticed that all the almost certain cases of our series were recorded after injection of lidocaine. This agent is the most documented for anaphylactic reaction in dental practice [24–27].

Severe anaphylactic reactions of grade III were the most frequently reported in this study (57.69% of all ADRs) but this rate decreased to 30.76% when focusing on dental practice. This is in accordance with data previously reported in medical practice [28]. It may be that, in dental practice, the

Table 7 Contents of local anesthetic solutions (available in France) and their allergic potential: adapted from Sambrook PJ et al. [4]

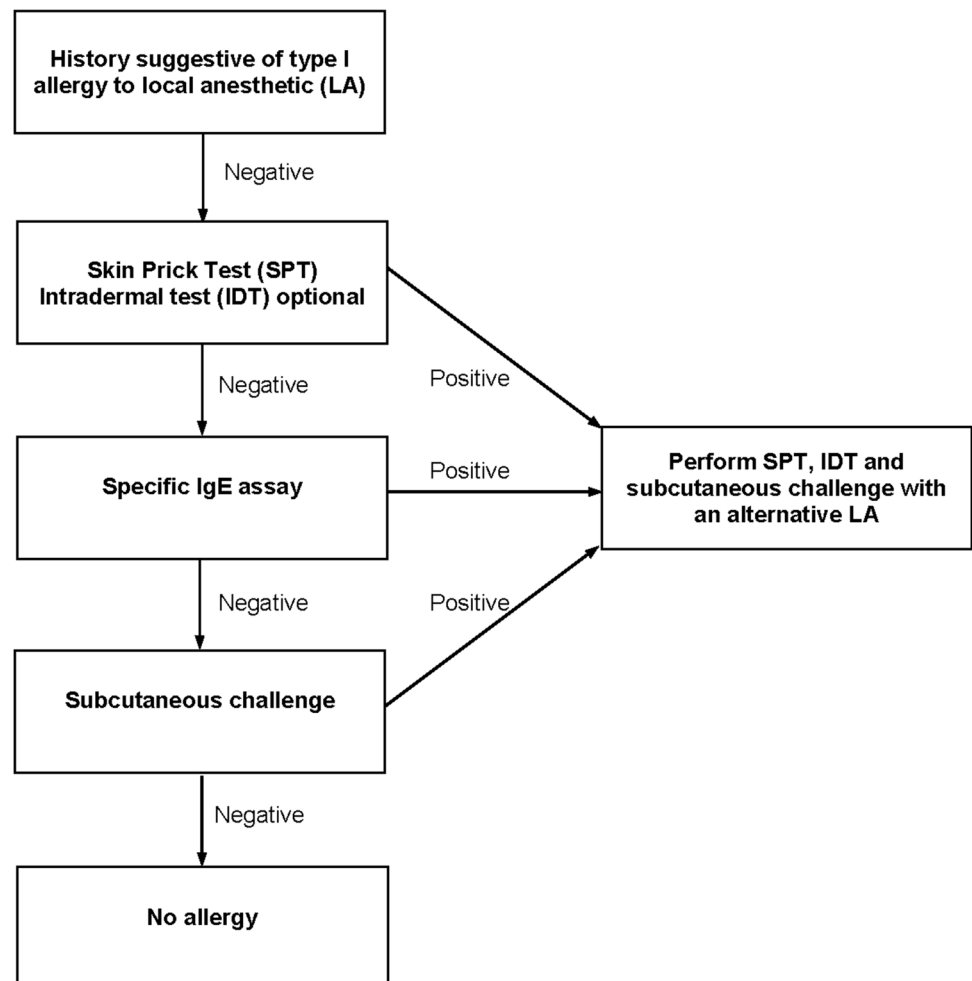
Component	Allergic potential
Anesthetic molecule	
- Ester-type LA: procaine	High risk of allergy
- Amide-type LA	All very low risk of allergy ($<1\%$ of all adverse reactions)
• Lidocaine	
• Prilocaine	
• Articaine	
• Mepivacaine	
Vasoconstrictor	No allergic potential (may result in cardiovascular responses)
• Epinephrine	
• Norepinephrine	
• Felypressin	
Antioxidant: sodium or potassium bisulfite	Low but most likely allergen in local anesthetic
Latex plugger and diaphragm	Theoretical risk but not clinically significant

LA, local anesthetic

patients had mostly nonsignificant medical histories compared with patients managed in hospital. Another interesting point highlighted in our study concerns the two cases of possible

cross-reactivity between amide-type LAs, lidocaine and ropivacaine or articaine (cases 7 and 13). The occurrence of such cases has been previously described in type I allergic reactions [28, 29]. Such cross-reactivities support the investigation of alternative LA agents when testing is performed.

In dentistry, anaphylaxis may also theoretically occur to the various constituents of a LA cartridge and could be related to other agents than the LA itself (Table 7) [4]. Of the components usually present in dental LA cartridges, it is reported that the most likely allergen is the preservative metabisulphite, which is added as an antioxidant in a number of formulations that contain a vasoconstrictor [4]. Antioxidants, mainly sodium or potassium bisulfite added to anesthetic solutions containing vasoconstrictors, can cause allergic reactions [30]. Another component, methylparaben, added as a bacteriostatic agent to maintain the sterility of the anesthetic solution, is known to cause severe allergic reaction with an approximate incidence of 2% [31]. But the use of this agent was banned in dental cartridges in the USA as early as 1984 and since the early 2000s, it has also been banned in Europe. Theoretically, there is a risk of latex allergy due to the latex plugger and diaphragm in the cartridge; however, this

Fig. 3 Algorithm for evaluation of suspected type I allergy to local anesthetic: adapted from Peroni et al. [29]

risk is not clinically significant [4]. Moreover, LA cartridges available in France, just as in many other countries, are now manufactured and packaged as part of a 100% latex-free process. In our study, no anaphylaxis to another component than anesthetic agent itself was recorded.

Given the rarity of true IgE-mediated reactions to LA, an appropriate investigation should be performed when a LA allergy is suspected. A standard of care committee of the British Society for Allergy and Clinical Immunology (BSACI) described the investigation processes for suspected anaphylaxis during general anesthesia. It stipulated that due to the rarity of true LA allergy, it is not possible to validate SPT and IDT. Therefore, after such tests, it is recommended to proceed with specific IgE assays and incremental subcutaneous challenge as required/appropriate [32]. In line with current guidelines, an algorithm for evaluation of suspected type I allergy to LA could be proposed (Fig. 3) [33].

It is essential to note that in the FDPS, causality assessment is made for each drug-ADR by a trained medical doctor or pharmacist and not by the health professional reporting the case or by the patient, as occurs in other countries. In this study, causality assessment was established in 4 of the 26 anaphylactic reactions recorded in dental practice.

A main problem with characterizing anaphylactic ADR in our patient series in dental practice was the number of drugs known to be allergenic that were involved in some reports, amoxicillin in particular in five cases. However, it should be noted that in three of these cases, the first-line allergy test results were negative for amoxicillin and not available for the others two.

Intramuscular antihistamine drugs are very effective in the treatment of anaphylaxis of grade I or II severity combined with prednisolone or prednisolone derivatives. In most severe cases, an initial subcutaneous or intramuscular injection of 10 mg epinephrine is used for resuscitation and to normalize vital signs [34]. This management approach was used in the most severe case in our series (case 24) with cardiac arrest. If necessary, additional doses of 5 or 10 mg could be injected again.

Our study has a number of unavoidable methodological drawbacks, as do most pharmacovigilance studies examining spontaneous report. Reporting by health professionals is entirely voluntary and not all ADRs are reported, while those that are reported may omit relevant data (such as detailed medical histories or allergic testings), or they may be confounded by other factors. Many authors speculate that the prevalence of ADRs is underestimated as a result of under-reporting [35–37]. In France, it has been estimated that less than 5% of all ADRs are spontaneously reported to the FPDS [36]. Moreover, healthcare professionals are more likely to report a severe or fatal suspected ADR than a nonserious reaction [38]. In addition, our results are based on a number of only 4 almost certain cases and 1 probable, whereas the majority of them were assessed as possible (14 cases) or doubtful (7 cases). We must also note that the retrospective nature of this study also

hinders its ability to obtain complete data, leading to potential inadequate or incomplete documentation. Moreover, the external validity of our study is quite limited and the lack of a control group makes impossible any possible inference on the associated risk factors. Consequently, based on the available data, we can only speculate about the true incidence of anaphylactic reactions to LAs in dental practice.

Conclusion

All these findings along with our results highlight the very low incidence of type I-IgE-mediated reactions to LA, particularly in dental practice. But true anaphylactic reactions to LA agents in dental practice do exist and can justify an in-depth investigation. In our study, the incidence rate of LA anaphylactic episodes in dental practice was estimated as 0.0261 anaphylactic episodes per million LA cartridges. In cases where an allergy is suspected, it is important to perform a thorough investigation because of the risk of the patient developing anaphylaxis. Testing appropriate alternatives for tolerance is of major importance in order to establish alternative LA options that have been challenged for clinical safety.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study was carried out with data of the FDPS, was anonymous and did not require ethical approval according to French legislation.

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