

## ORIGINAL REPORT

# Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing<sup>†</sup>

Régis Fuzier MD, PhD<sup>1,2\*</sup>, Maryse Lapeyre-Mestre MD, PhD<sup>1</sup>, Paul-Michel Mertes MD, PhD<sup>3</sup>, Jean-François Nicolas MD, PhD<sup>4</sup>, Yves Benoit MD<sup>5</sup>, Alain Didier MD, PhD<sup>6</sup>, Natalie Albert MD<sup>7</sup> and Jean-Louis Montastruc MD, PhD<sup>1,8</sup> and the French Association of Regional Pharmacovigilance Centers

<sup>1</sup>Laboratoire de Pharmacologie Médicale et Clinique, Unité de Pharmacopépidémiologie EA3696, Faculté de Médecine, Université de Toulouse, Université Paul Sabatier, Toulouse, France

<sup>2</sup>Pôle d'Anesthésie-Réanimation, Service d'Orthopédie, CHU de Toulouse, Hôpital Purpan, Toulouse cedex, France

<sup>3</sup>Service d'Anesthésie-Réanimation Chirurgicale, U684, Hôpital Central, CHU de Nancy, Nancy, France

<sup>4</sup>Service d'Immuno-Allergologie, Pierre-Bénite cedex, France

<sup>5</sup>Service Allergo-Anesthésie, CHU Edouard Herriot, Lyon cedex, France

<sup>6</sup>Service de Pneumo-Allergologie, Clinique des Voies Respiratoires, CHU de Toulouse, Hôpital Larrey, Université de Toulouse, Toulouse cedex, France

<sup>7</sup>Staff Anesthesiologist, Department of Anesthesia, Laval University Hospital, Quebec, Canada

<sup>8</sup>Service de Pharmacologie Clinique, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacopépidémiologie, et d'Informations sur le médicament, CHU de Toulouse, Toulouse, France

## SUMMARY

**Purpose** Amide type local anesthetic agents are among the most commonly used drugs in medicine. Several adverse drug reactions (ADRs) have been previously described with their use. Among them, allergic reactions are considered rare. The aim of this study was to describe the main characteristics of ADRs induced by amide type local anesthetic drugs.

**Methods** We studied reports recorded in the French Pharmacovigilance database and the GERAP database over a 12-year period (1995–2006). For each report, we detailed the clinical features and skin tests used. Delayed or immediate-type allergic reactions and cross-reactivity between amide type local anesthetics were also analyzed.

**Results** We identified 16 reports (seven from the Pharmacovigilance database and nine from the GERAP database). Local anesthetic allergic reactions occurred mostly in young females (F/M sex ratio = 14:2). An immediate-type allergic reaction was encountered in 11/16 cases. Lidocaine was the local anesthetic most often involved (11/16). Prick test, intradermal reaction, and challenge tests were used to confirm the diagnosis. A cross-reactivity between the different amide type local anesthetics was found in six cases (lidocaine–mepivacaine in all cases).

**Conclusions** This is the largest series of immediate-type local anesthetic allergic reactions reported in the literature. Cutaneous symptoms are the main features even though more serious symptoms may occur. Intradermal reaction and challenge tests are very helpful. Because cross-reactivity is not scarce, skin tests should involve several local anesthetics. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS—allergic reactions; local anesthetics; skin tests

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## INTRODUCTION

True allergic reactions to local anesthetics (LAs) are very rare adverse reactions when compared to myorelaxant or

latex allergies. At the most, they represent less than 1% of all adverse LA reactions.<sup>1–3</sup> They have mainly been described with ester type LAs. However, allergic reactions to LAs have been documented even with amide type LAs. Contact dermatitis (type IV reaction) is the most often reported allergic reaction to several amide type LAs.<sup>4–8</sup> Adverse LA-induced reactions by IgE-mediated allergic mechanisms (type I reaction: anaphylactic shock or urticaria) are still debated.<sup>9–12</sup>

\* Correspondence to: Dr R. Fuzier, Pôle d'Anesthésie-Réanimation, Service d'Orthopédie, Hôpital Purpan, Place Dr Baylac, TSA40031, 31059 Toulouse cedex 9, France. E-mail: fuzier.r@chu-toulouse.fr

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Therefore we decided to evaluate data to address current reported incidents of amide type LA reactions.

The aim of this paper was to report amide type LA allergic reactions that were documented with a clear and detailed medical history (description of the reaction) and a positive skin test in order to define their main clinical, allergic, and pharmacological characteristics. The evaluation was conducted in France over a 12-year period.

## METHODS

For the purpose of the final analysis, we combined reports from the French Pharmacovigilance database and the GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: study group of perianesthetic anaphylactoid reactions) database.

### *French pharmacovigilance database*

The French Pharmacovigilance database was established in 1985 to register spontaneous reporting of adverse drug reactions (ADRs). By law, every prescriber must report 'serious' or 'unexpected' ADRs to their French Regional Pharmacovigilance Center. In the present study, we studied ADRs reported to the French Network of Pharmacovigilance Centers (and recorded into the French Pharmacovigilance database) occurring between 1 January 1995 and 31 December 2006. Among the 21 0017 ADRs reported during this period, we selected those in which one of the five amide type local anesthetics (lidocaine, bupivacaine, ropivacaine, levobupivacaine, and mepivacaine) was suspected as causing an allergic reaction. Among these retrieved reports, a specific analysis was then performed. All reports with either a positive skin test to another drug and/or a negative skin test to LAs were eliminated. We used the imputability scoring system routinely used in the French Pharmacovigilance database. By imputability we mean the assessment of the probable responsibility of a drug in the development of an undesirable effect. This is measured by the French imputability method based on the time of onset, the course of the reaction ('C' = Chronological subscore), risk factors, and screening for other causes ('S' = Semiological subscore). According to the values of these two subscores (C and S), intrinsic imputability (I) is classified into five levels (I0–I4): 'unlikely', 'possible', 'probable', 'likely', and 'very likely'.<sup>13</sup> Thus, for the final analysis, we considered only reports with an imputability score superior or equal to 1 (relation with drug at least 'possible'). We selected and analyzed only reports with both an accurate medical description of the

reaction and a positive skin test and/or a positive challenge test. In order to complete these reports, we contacted, when necessary, every Pharmacovigilance regional center that had recorded the selected reports to obtain more information. From these reports, we noted the date of the ADR, patient age and gender, type of LA, type of clinical symptoms, 'seriousness' and outcome<sup>14</sup> as well as skin testing results. Reports were classified according to the type of reaction (i.e., immediate and delayed allergic reactions). For immediate-type allergic reactions, a classification based on symptom severity was applied (as described by Mertes<sup>1</sup>). This is a 5-grade classification for quantification of the anaphylactoid reaction. Grade I corresponds to cutaneous signs (generalized erythema, urticaria, and angio-oedema). Grade II describes measurable but non-life-threatening symptoms (cutaneous symptoms, arterial hypotension, tachycardia, respiratory disturbance, cough, and difficulty to inhale). In Grade III, life-threatening symptoms occur (collapse, tachycardia or bradycardia, and bronchospasm). Grade IV corresponds to a cardiac and/or respiratory arrest and grade V to death. Time between LA injection and occurrence of symptoms was also noted and taken into account. We defined an allergic reaction as immediate and delayed (or semi-delayed) when symptoms occurred within or beyond 1 hour after the LA injection, respectively, in accordance with the European Academy of Allergy and Clinical Immunology (EAACI) definitions.<sup>15</sup>

### *GERAP database*

GERAP is a network of 42 French allergeo-anesthesia outpatient clinics. The aim of this network set up in 1985 was to collect all immediate allergic reactions occurring with drugs involved in the anesthetic procedure.<sup>2</sup> These reactions were recorded into the GERAP database. The protocol included a questionnaire about the patient's age, gender, number of previous anesthetic procedures, history of allergy, date of the reaction, and drugs used before the reaction occurred. Details were obtained about the degree and severity of the reaction, graded using the aforementioned classification. Information about the allergy investigation was also systematically recorded: date of incidence, type of skin tests performed, dilution of the tested drug leading to a positive reaction, cross-reactivity, results of histamine, and tryptase monitoring during the adverse reaction when available. Only reports in which the LA was positively determined as the cause of the allergic reaction were kept for final analysis.

Data are expressed in means  $\pm$ SD or as numbers with percentages in brackets.

## RESULTS

*Pharmacovigilance database*

21 0017 ADRs were registered in the database between 1995 and 2006. Among these reports, we identified 286 reports in which an LA was suspected as the cause of the allergic reaction. Among the 286 reports, seven were selected because of a contributive medical history associated with either a positive skin test result or the presence of the LA as the sole drug involved. After contacting the different French Pharmacovigilance centers, these seven reports were analyzed.

The seven LA allergic reactions analyzed were all reported after 2001 (Table 1, cases 1–7). Six cases occurred in female patients and one in a male patient. Mean age was  $43 \pm 13$  years.

According to clinical features and skin tests, immediate allergic reactions were found in three cases (case numbers 1, 2, and 7, Table 1). Cutaneous eruptions were the main symptoms. An anaphylactic shock occurred in one case of immediate allergic reaction with mepivacaine

(case no. 7, Table 1). Occurrence of symptoms varied from minutes to one month. Local anesthesia was the most common route of administration although cases using epidural (two cases) and brachial plexus routes (one case) were also reported. Outcome was favorable in all cases.

Allergic screening was performed either with the drug involved in the allergic reaction or sometimes with another amide type LA. Allergic screening included skin tests (patch test and/or prick test and/or intradermal reaction) and/or challenge tests. Histamine release testing was performed in two cases. Allergic screening results are summarized in Table 2. Patch tests ( $n = 3$ ), intradermal reaction tests ( $n = 4$ ), and challenge tests ( $n = 2$ ) were the most oftenly performed. Positive allergic screening (histamine release testing and/or immediate positive reaction to prick test or IDR and/or challenge test) where there was a positive test result for several LA agents belonging to the amide group occurred in three cases. This suggests a cross-reactivity among LA agents in the amide group.

Table 1. Main characteristics of the LAs' allergic reactions from the French Pharmacovigilance database (1–7) and GERAP group (A–I)

Observat. number	Year	G	Age	Drugs associated	LA	Route of Admi	Clinical symptoms	Timing of LA administration	Grade	Imput
1	2001	F	63	Hexamidine	L	L. Inf	Quincke Edema	<1 hour	II	3
2	2001	F	42	—	L	L. Inf	EdemaDiscomfort	<1 hour	I	3
3	2004	F	35	—	L	Epid. A	Papule Vesicle Pruritus	6–12 hour maximum 24–48 hour until 5 d	DAR	4
4	2002	F	36	—	L	L. Inf	Erythema Pruritus	3 d	DAR	1
5	2004	F	24	—	L	Epid. A	Late eczema	1 mo until 1 mo	DAR	4
6	2001	F	54	—	M	L. Inf	Urticaria	1 d until 3–4 d	DAR	4
7	2005	M	50	Midazolam Sufentanil	M	PNB	An. Shock Total rash Bronchospasm Cyanosis	<1 hour	III	4
A	2001	F	24	—	A	L. Inf	Discomfort Pruritus Vomiting Sweats	—	II	NA
B	2000	F	26	—	L	L. Inf	Urticaria	—	I	NA
C	1998	M	15	Propofol	L	L. Inf	Erythema Vesicle	—	I	NA
D	—	F	65	—	B	—	Urticaria	—	II	NA
E	—	F	38	—	M	—	Hypotension Urticaria	—	II	NA
F	2006	F	20	Propofol Remifentanil Ketamine Desflurane Tramadol	L	L. Pulv	Hypotension Cough Erythema Tachycardia Hypotension Bronchospasm	<1 hour	III	NA
G	2006	F	44	—	A	L. Inf	Eczema Edema	<1 hour	I	NA
H	—	F	—	—	L	L. Inf	Local then generalized edema	<1 hour	I	NA
I	1998	F	54	—	L	L. Inf	Erythema Edema	24 hour	DAR	NA

Observat. number = observation number, G = gender, LA = type of local anesthetic (L = Lidocaine, M = Mepivacaine, A = Articaine, B = Bupivacaine); Route of admi = administration route of LA (L. Inf. = local infiltration anesthesia, Epid. A = epidural anesthesia, PNB = peripheral nerve block, L Pulv = local pulvization); Grade: DAR = delayed allergic reaction. In case of immediate allergic reactions, a symptom classification method was used (Grade I = cutaneous signs (generalized erythema, urticaria, angio-oedema), grade II = measurable but non-life-threatening symptoms (cutaneous signs, hypotension, tachycardia, respiratory disturbance, cough, difficulty to inhale), grade III = life-threatening symptoms (collapse, tachycardia or bradycardia, bronchospasm), and grade IV = cardiac and/or respiratory arrest). An. Shock = anaphylactic shock. D = day, mo = month. Imput = intrinsic imputability (1 = possible, 2 = probable, 3 = likely, 4 = certain, NA = not applicable) evaluated according to Reference.<sup>16</sup>

Table 2. Different skin tests used in the reports from the French Pharmacovigilance database (1–7) and GERAP group (A–I) enabling the diagnosis of an LA allergic reaction

N	LA tested	Patch test	Prick test	Intradermal reaction	SC challenge	Histamine release testing
1	Lidocaine					Neg
	Mepivacaine					+
	Articaine					Neg
2	Lidocaine				+	
	Mepivacaine				+	
	Bupivacaine				+	
3	Lidocaine	+		Neg		
	Bupivacaine	Neg		Neg		
	Ropivacaine	Neg		Neg		
4	Lidocaine	Neg	Neg	+		
	Mepivacaine	Neg	Neg	+		
	Bupivacaine	Neg	Neg	Neg		
	Ropivacaine	Neg	Neg	Neg		
5	Articaine	Neg	Neg	Neg		
	Lidocaine	+				
	Bupivacaine	Neg				
6	Articaine	Neg				
	Mepivacaine			Neg	+	
7	Lidocaine		NA	+		+
	Mepivacaine		+	+		+
	Ropivacaine		Neg	Neg		
	Bupivacaine		Neg	Neg		
A	Articaine			+		
B	Lidocaine			+	+	
C	Lidocaine			+		
D	Bupivacaine			+		
E	Mepivacaine			+		
F	Lidocaine			+		
	Mepivacaine			+		
	Ropivacaine			+		
	Bupivacaine			–		
G	Articaine			+		
	Lidocaine			–		
	Mepivacaine			–		
H	Lidocaine		+	+		
	Mepivacaine		+	+		
	Bupivacaine		–	–		
	Articaine		–	–		
I	Lidocaine	+				
	Mepivacaine	+				
	Articaine	–				
	Bupivacaine	–				
	Ropivacaine	–				

Neg = negative test result; + = positive test result; NA = not applicable.

### GERAP database

From GERAP database, we identified nine reports in which an LA was the cause of the allergic reaction (Table 1, cases A–I). They occurred in eight female patients and one male patient (mean age  $36 \pm 13$  years).

Lidocaine was the most often LA involved (five cases) followed by articaine (two cases), bupivacaine (one case), and mepivacaine (one case).

Local anesthesia was the only reported route of administration in these nine cases.

According to clinical features and skin tests, immediate allergic reactions were noted in eight cases (cases A–H).

Cutaneous signs (erythema, urticaria, and edema) were the predominant clinical features. In one case, the allergic reaction was considered as 'serious' (grade 3, case no. F). The outcome was favorable in all cases.

Allergic screening results are presented in Table 2. A cross-reactivity between amide LAs was declared in three cases.

### DISCUSSION

To the best of our knowledge this paper presents the largest series published in the literature (history and

positive skin tests) of amide LA ADRs. The high number of immediate-type allergic reactions (11/16 cases) strengthens the results of this study. Even though such reactions are often considered as rare, one must keep in mind that such ADRs can occur. It is therefore mandatory to confirm the diagnosis in order to avoid future use of these drugs in such allergic patients.

LA agents are among the most commonly used drugs in medicine. A variety of ADRs has been reported. Acute disorientation or seizures may occur after overdosing or inadvertent intravenous injection. In addition, many local anesthetics contain adrenaline or other excipients such as anti-oxidants or preservatives (bisulphites, parabens, carboxymethylcellulose, and para-aminobenzoic acid). Local anesthetics can also produce sympathetic effects (tachycardia, arterial hypertension,...) irrespective of the presence or absence of vasoconstricting agents.<sup>16</sup> Immunological reactions to local anesthetics, particularly the newer amides, remain anecdotal and symptoms usually result from vasovagal episodes or anxiety reactions.<sup>16</sup>

In many cases, medical history is not sufficient to definitively prove LAs' allergic reactions, even after strict anamnesis and physical examination. Different diagnostic protocols have been proposed in the literature,<sup>11,16</sup> but it would seem that both clinical history and skin testing results are necessary to confirm LA-induced reactions.<sup>1,16</sup> This is why we intentionally decided to report only cases with both a clear clinical history and a positive skin test result. We also decided to focus on cross-reactivity between amide-type LAs because this point is still disputed in the literature.

In our work, LAs allergic reactions occurred mostly in young people. Female gender was involved in the majority of cases (14/16 cases). These results are in accordance with previous studies focusing on allergic reactions after an anesthetic procedure.<sup>1,2</sup> Lidocaine was the most often LA involved in such reactions, probably because this LA is the most often used in medical practice.<sup>17</sup>

True type I allergic reactions are uncommon (fewer than 1%) and have not been well documented in the literature.<sup>10,11,18–20</sup> In the largest French survey reporting the incidence of anaphylaxis during anaesthesia over a 2-year period, LAs were involved in only 1 case (0.2%).<sup>2</sup> Our study gathered 11 immediate-type allergic reactions after LA injection, even though challenge tests have not been performed in all cases. This is, to our knowledge, the largest published report on the subject. It is interesting to note that all amide type LAs were involved and this while using different routes of administration (epidural and local anesthesia, peripheral nerve blocks). In the retained cases, the first

symptoms occurred within 1 hour after administration and, as opposed to delayed-type allergic reactions, clinical features were not limited to cutaneous signs. Indeed, systemic signs, including neurological, respiratory, and cardiovascular symptoms were reported. Urticaria, angioedema, bronchospasm, cardiovascular depression, and in severe cases shock are the main symptoms in immediate-type 1 reactions.<sup>21</sup> However, it is interesting to note that urticaria and angioedema might be initiated by a delayed-type T-cell mediated immune reaction, as had occurred in case no. 6 (Table 1). In this case, intradermal testing was negative (Table 2). This is in accordance with data published by Orasch *et al.*<sup>20</sup>. As described above, anamnesis and reported symptoms were not sufficient to confirm the diagnosis of the allergic reaction. Thus, skin tests are mandatory as additional tools. Different causes have been advanced to explain the difficulty in diagnosing true potential allergic reactivity: the history of the prior reaction may be vague or equivocal and the lack of identification of the actual specific LA hapten-carrier complex limits the potential usefulness of immunological tests.<sup>3</sup> Under such conditions, skin tests (prick test, intradermal test) or incremental challenges are proposed. Choosing the appropriate test and the order of their use remains controversial. As seen in Table 2, some centers used prick tests as the first skin tests whereas others used more first intradermal reaction tests or subcutaneous challenges. Intradermal testing has been used in the majority of studies, although few studies have demonstrated that prick testing has a similar efficacy.<sup>22</sup> For some authors, skin prick test can be used as a starting test with the suspected drug.<sup>16</sup> This then may be followed by an intradermal test and/or a subcutaneous test when relevant or when skin prick testing remains negative or equivocal. For others, intradermal tests may be omitted because it appears to produce more false-positive reactions than prick tests.<sup>21</sup> Cutaneous provocation tests with the drug involved and alternative local anesthetics could complete the procedure in case of negative results in skin prick and intradermal tests.<sup>16</sup> For others, intradermal skin tests are the best starting procedures.<sup>10</sup> Finally, there is probably no significant difference in the reliability of diagnosis of intradermal or prick testing. If the results of either test are negative or equivocal, other tests should be performed. Interpretation of skin results is probably the most important factor when diagnosing true allergies.

Allergic reactions after LA injections have usually been described as contact dermatitis. We reported five delayed-type allergic reactions in our study (case numbers 3, 4, 5, 6, and I, Table 1). Clinical features

were most often cutaneous signs (erythema, pruritus, urticaria, and eczema) and occurred between 6 hours and 1 month after LA administration. This is in accordance with data published in the literature, even though the delay in case 5 (1 month) could be questioned. However, the imputability score was I4 (very likely) and, as previously described, it was calculated by an independent physician. Thus, we decided not to delete such report. Edema is usually a symptom encountered in immediate-type hypersensitivity. However, as shown in Table 1 (case no. I), delayed-type hypersensitivity may lead to edema. This explains why it may be difficult to differ between type I and IV reactions. However, because other mechanisms may be involved in clinical features occurring after such a long time postoperatively, imputability score becomes one of the main parameters to characterize the implication of the LA. In our series, imputability score was high in almost all cases (3 or 4, Table 1). Delayed-type allergy to injected LAs is clinically characterized by local swelling, which develops within 2–24 hours and generally lasts for several days.<sup>19</sup> In our study, two LAs (lidocaine and mepivacaine) were involved in this type of allergic reaction. The administration route of the LA was either local or epidural anesthesia. All amide-type LAs have previously been involved in delayed-type reactions.<sup>4,6–8,23</sup> However, proving the imputability of the LA in such a reaction remains challenging. In an analysis of 197 reported adverse reactions after LAs injection, Gall *et al.* were able to prove delayed-type allergic response in only one case.<sup>19</sup> In conjunction with medical history, skin tests are often necessary to properly diagnose delayed-type allergic reactions. As confirmed in our present study this type of reaction is best proven by patch testing, which may be considered as the gold standard for delayed-type allergy.<sup>21</sup> However, the risk of false positive reaction must be kept in mind (patch-induced skin irritation).

Another interesting point highlighted in our study concerns the six cases of cross-reactivity between amide-type LAs. Cross-reactivity is well established between ester-type LAs. Because allergy to amides has only seldomly been verified, the cross-reaction pattern between amide anesthetics is not well known. The occurrence of some cases has been previously described not only in cases of contact dermatitis, but also in cases of type I allergic reactions.<sup>10</sup> In our study, four of the six cross-reactivity cases were described in cases of type I allergic reaction (cases 2, 7, F, and H, Table 2). Cross-reactivity between lidocaine and mepivacaine was reported in all cases. Ropivacaine and bupivacaine associated with lidocaine–mepivacaine were described in one case as was previously published.<sup>4,7,23</sup>

It is important to note that our study tends to confirm the lack of cross-reactivity between articaine and other amide-type LAs (cases 1, 4, 5, A, G, H, and I, Table 2). Articaine is an amide, but has a substitute thiophen ring, whereas all amino acylamides have a methylated phenyl ring. This difference may explain the lack of cross-reactivity of articaine.<sup>23</sup>

The main limit of our study concerns the lack of exhaustivity and the heterogeneity encountered with the two sources of data: the French pharmacovigilance system and the GERAP group database. The French pharmacovigilance system was established to register spontaneous reporting of ADRs. Even though by law all ADRs should be reported to the Pharmacovigilance System, Begaud *et al.* estimated that only 5% of serious ADRs are declared.<sup>24</sup> However, spontaneous reporting of ADRs remains the most frequently used and efficient method to identify new ADRs after drug approval. Even though the reporting rate in France is one of the highest among European countries (reporting rate of 389.7 reports/10<sup>6</sup> population per year),<sup>25</sup> the main limit of this series is that it is hampered by both quantitative and qualitative underreporting. To improve the number of complete reports, we used the GERAP group database.<sup>26</sup> This group specifically focused on allergic reactions occurring after anesthetic procedures. A specific protocol is validated for each procedure. Only reports that are completed enter the database. This may explain why type I allergic reactions mainly came from this source. Studies underlined the interest of merging data from different databases to identify fully the real impact of ADR. The capture–recapture method is often used in such circumstances.<sup>27</sup> Unfortunately because no common cases could be identified, this method was not applied in order to estimate the real number of ADRs occurring during the study period.

In conclusion, even though true allergic reactions to LAs are rare, they are documented even with amide-type LAs. For the first time, we report an important series of such reactions. The type of clinical features and skin tests used to distinguish delayed-type and immediate-type allergic reaction are discussed.

#### KEY POINT

- The occurrence of an allergic reaction, and particularly immediate-type reaction to amide type local anesthetics is often considered as rare. In this paper, we report one of the largest series of true allergic reactions after local anesthetics administration. Clinical features and skin tests used as well as cross-reactivity between such drugs are detailed.

Because LAs are among the most commonly used drugs in medicine, establishment of a proper procedure is relevant for patients. Indeed, for the affected (or concerned) patients a list of LAs that should be definitely avoided or those that are permitted for further care must be clearly stated. The risk of cross-reactivity between amide-type LAs must be kept in mind when performing skin tests.

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