

# HYPERSENSITIVITY TO LOCAL ANAESTHETICS – 6 FACTS AND 7 MYTHS

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## ABSTRACT

Local anaesthetics (LAs) are commonly used drugs. In spite of their widespread use, true hypersensitivity appears to be very infrequent. In fact most of the adverse reactions are due to pharmacological, toxic or vasovagal effects of LAs.

Our review of the literature has shown that true allergy to LA is in fact exceptional. Skin tests for LA allergy, including skin-prick tests (SPT) and intradermal (ID) tests, have poor sensitivity and specificity. True LA allergy, when appropriate, has to be confirmed by challenge. Provocation challenge is safe and well tolerated.

Since the discovery of the anaesthetic effect of cocaine in 1884, local anaesthetics (LAs) have been widely used. It has been estimated that 6 million people are injected with LAs each day around the world. In spite of their widespread use, true hypersensitivity appears to be infrequent. However the perception of allergy to LA among the general public is high. In our drug allergy clinic, referrals for LA allergy are in the same range as penicillin or aspirin allergy referrals.

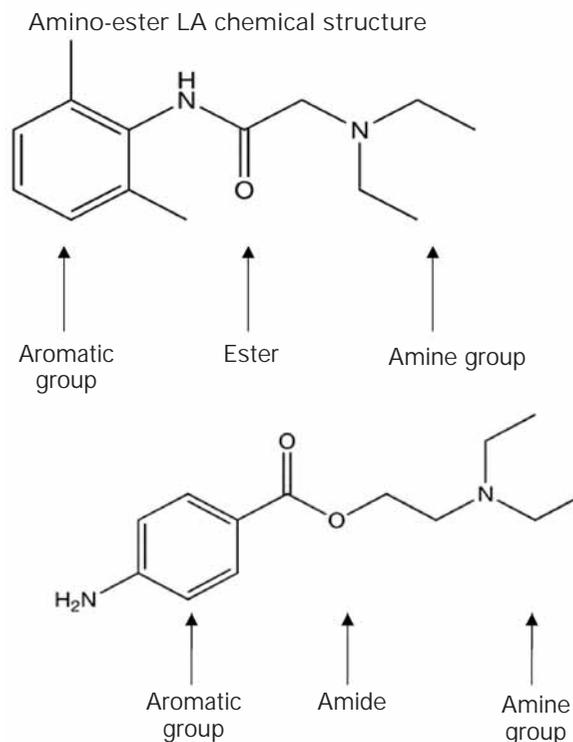
In this review, based on published literature (PubMed-Medline and EMBASE) as well as our own experience, we attempt to explain some of the facts and reject some of the myths surrounding allergy to LA.

LAs have two different chemical structures, which define two different families, either amino-ester or amino-amide. The ester family includes cocaine, procaine, tetracaine, all spelt with a single 'i' while in the amide family, each individual name contains two 'i's e.g. lignocaine, prilocaine, bupivacaine.

LAs reversibly interrupt impulse conduction along peripheral nerve axons. This effect is achieved by blockade of sodium channels. LA can be used topically or injected (subcutaneously, in the gum or around a nerve plexus or spinal cord for block anaesthesia, and epidural). Addition of epinephrine to LA delays its absorption by decreasing local blood flow and prolongs the duration of anaesthetic action. Associated vasoconstriction also decreases the peak plasma concentration and therefore the risk of generalised toxic side-effect. The chemical structure of the compound (Fig. 1) determines the duration and strength of the anaesthesia, for example bupivacaine is 16 times more potent than procaine. It also determines its metabolism and toxicity. It is therefore hardly surprising that it should also have an impact on the type of adverse drug reactions, including allergic reactions.

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The pharmacological differences between LAs make certain LAs more favourable than others for specific procedures, i.e. lignocaine is widely used for subcutaneous injection, and bupivacaine is preferred for epidural or gum injections.



Amino-amide LA chemical structure

Fig. 1. Chemical structure of amino-ester and amino-amide molecules.

## FACTS AND MYTHS

**Fact 1.** Risk of adverse drug reaction to LA may be increased in patients with deranged liver function or pseudocholinesterase dysfunction.

Ester-LAs are metabolised by pseudocholinesterase to p-amino-benzoic acid (PABA). The risk of adverse reaction is increased in patients with altered pseudocholinesterase function. Amide-LAs are metabolised in the liver; therefore patients with decreased hepatic function are at increased risk of overdose and toxic reactions.<sup>1</sup>

**Fact 2.** IgE-mediated hypersensitivity to LAs is extremely rare.

Globally the tolerance of LAs is good, with low incidence of adverse reactions. Two types of hypersensitivity are described with LAs – the relatively more common contact delayed hypersensitivity, mainly related to ester-LAs, and the less common immediate hypersensitivity associated with ester-LAs and exceptionally with amide-LAs. However, there is some doubt as to the reality of true allergic, IgE-mediated anaphylaxis

with amide-LAs.<sup>2</sup> Tsabouri *et al.*<sup>3</sup> found no IgE-mediated reactions in 157 patients referred with LA-associated adverse drug reactions. Similarly Gall *et al.*<sup>4</sup> tested 197 patients and found only 2 immediate-type reactions, which were also considered not to be IgE related.

**Fact 3. Sensitisation and cross-reactivity, resulting in delayed-type IV reactions, between ester-LAs are common.**

Sensitisation to topical ester-LA resulting in contact allergy is common. Moreover cross-reactivity between members of the ester family is usual. One of the most frequently used ester-LAs for topical applications is benzocaine. It is used in several types of products such as sun creams and haemorrhoid creams, as well as some topical anaesthetics. Its main derivative, PABA, is a common and potent sensitiser. It has been estimated that 5% of individuals who have applied benzocaine will become sensitised to it.<sup>5</sup> Other topical anaesthetics such as cocaine and tetracaine are based on the same PABA structure, which may lead to cross-reactivity.

**Fact 4. Patch testing is a reliable method of diagnosis of delayed-type IV hypersensitivity reactions.**

Type IV hypersensitivity (Gell and Coombs classification), e.g. contact dermatitis following exposure to LA, should be investigated by patch testing. However delayed inflammatory reaction may in rare cases develop following injection of LAs, eliciting localised delayed oedema at the site of the injection.<sup>6,7</sup> Contact dermatitis usually appears within 24 to 72 hours; it may, however, be clinically detectable as soon as 2 hours post exposure to LA.<sup>8</sup>

Patch testing for allergic contact dermatitis caused by LA is a good predictor of allergic type IV reactions<sup>9</sup> and it should be performed according to the guidelines of the International Contact Dermatitis Research Group.<sup>10</sup> Contact reactions to amide-LAs have been described, though infrequently.

**Myth 1. Amide-LAs are potent sensitisers and commonly cross-react with ester-LAs.**

Amide-LAs are rare sensitisers by topical application. Lignocaine used topically in gel or in cream does not cross-react with benzocaine when tested with epicuta-

neous patch test.<sup>11</sup> Topical cross-reactivity with other amide-LAs is described infrequently. Patch tests with lignocaine are positive in subjects with delayed sensitisation to lignocaine. The suggested concentration is 20% in petroleum for lignocaine<sup>12</sup>

Clinical-cross reactivity between type IV reactions to ester-LAs and type I reactions to amide-LAs has never been described. Ruzicka *et al.*<sup>13</sup> found that among 104 patients sensitised to ester only 3 had positive intradermal (ID) test results with amide although they had no history of reaction with amide-LA.

**Myth 2. Skin testing is a reliable tool when looking for LA allergy.**

Immediate-type hypersensitivity to esters was observed frequently in the past.

However, since the introduction of lignocaine in 1948 by Nils Lofgren, amide-LAs have been used for injection instead of ester-LAs, and as a result the incidence of immediate allergic reaction to ester LAs has dropped dramatically.

The value of skin testing to diagnose LA immediate hypersensitivity is controversial and it is sometimes bypassed altogether in favour of graded drug challenge.<sup>14,15</sup>

We reviewed the medical literature from the last 20 years focusing on sensitivity and specificity of skin testing with regard to challenge with LA. We found 9 series (Table I) which involved a total of 1 094 patients who suffered adverse reaction to LA and were assessed with skin testing and challenge.<sup>2,4,16-22</sup> Out of 1 094 patients only 3 suffered an immediate allergic reaction when LA was reintroduced. None of the 3 had positive SPT or ID results. In the same series, false-positive skin tests varied vastly in a range from 0% to 27%.<sup>2,4,16,19,22</sup>

After collating all these results, we can conclude that:

- Challenges were positive in 3 patients out of 1 094 with mild reaction at reintroduction, yet those 3 patients had negative skin tests. Skin tests are therefore a poor predictor of positive challenge.
- Skin tests may be positive in patients who are able to tolerate reintroduction of LA during challenge.
- Most of the adverse reactions are not allergic in nature but occur as a result of other mechanisms.

*Table I. Results of skin testing (SPT, ID) and provocation challenge in published series of suspected allergic reactions to LA*

Authors	Year	No of pts	Skin tests +	Challenge	Comments
	SPT; IDT				
Incaudo <i>et al.</i> <sup>16</sup>	1978	59	5/59	0/50	
De Shazo & Nelson <sup>17</sup>	1979	90	0/90; 10/90	0/84 (4 IDT +)	IDT dilute positive but IDT neat negative
Fisher & Graham <sup>18</sup>	1984	27	1/27	0/26	
Le Sellin <i>et al.</i> <sup>19</sup>	1986	25	0/25	1/25	1 hand oedema
Chandler <i>et al.</i> <sup>20</sup>	1986	59	0/59	0/59	2 anaphylactic histories had negative challenge
Escolano <i>et al.</i> <sup>21</sup>	1990	35	0/35	0/35	
Gall <i>et al.</i> <sup>4</sup>	1996	177	0/177	3/143	1 delayed, 2 local immediate reactions (non IgE mediated)
Troise <i>et al.</i> <sup>2</sup>	1998	387	13/386; 3/13	0/386	8 subjective reactions
Berkun <i>et al.</i> <sup>22</sup>	2003	236	0/236; 0/236	1/236	1 local erythema in patient with negative skin test

SPT – skin-prick test, ID – intradermal

- Provocation challenge is safe and well tolerated.
- Based on the available literature, specificity and sensitivity of skin tests to LA are of questionable value.

According to the European Network for Drug Allergy (ENDA) guidelines, diagnosis has to be confirmed in both groups of patients – those who tested positive and those who tested negative on skin tests, with graded challenge after cautious balance of individual benefit.<sup>23</sup>

### Myth 3. Sensitivity of intradermal skin testing with LAs is high.

Reviewing the literature for evidence of positive challenges after reintroduction of LA in subjects with history of immediate reaction to LA, we found 4 anecdotal case reports with only 5 positive challenges.<sup>24-27</sup> SPTs were negative in 4 cases but ID tests were positive in 3 cases and negative in 2, although 1 subject suffered severe anaphylaxis at introduction of ropivacaine with negative ID test. In addition, from the series of Gall and collaborators,<sup>2</sup> patients had itchy wheals and erythema at the test sites and also on the trunk shortly after exposure to lignocaine or articaine. Those patients had negative ID 1/10 tests. When we collated all the results of 7 positive challenges, we found that SPTs were negative 6 times out of 7, ID tests were negative 4 times out of 7.

To summarise, in the small group of patients who suffered allergic reaction to LA confirmed by positive challenge, the sensitivity of ID tests is low (43%), and sensitivity of SPT even lower (14%). Negative skin tests may not predict tolerance. Patients sensitised to one amide-LA may be sensitised to one of several other amide-LAs.

### Myth 4. Adverse reactions to LAs are often related to paraben preservatives.

Parahydroxybenzoates are well known contact sensitizers and their use can result in delayed-type hypersensitivity reaction; however their association with immediate reactions to LAs has been debated. Simon *et al.*<sup>28</sup> in 1984 recorded only 3 cases with immediate-type, rare IgE-mediated reactions. Skin testing for immediate-type reactions also appears to be of poor value, because of 5 patients with positive skin test results, reported by Gall *et al.*,<sup>4</sup> all were able to tolerate reintroduction of paraben-containing LA.

### Myth 5. Parabens are commonly used preservatives in injectable LAs.

Parabens as a potential cause of reaction to LA have become less significant since fewer injectable LA preparations contain it as an ingredient. In our practice (UK) only a few preparations contain parabens, e.g. Xylocaine 1% and 2%, and Citanest.

### Myth 6. Sodium metabisulfite contained in some of the LAs is a common cause of adverse drug reaction.

Sodium metabisulfite is included in LAs containing epinephrine to prevent oxidation. The concentration of sulphite in these preparations ranges from 0.375 mg/ml to 0.5 mg/ml. Sulphite sensitivity primarily affects a small subgroup of the asthmatic population.

Clinical history of metabisulfite allergy is often misleading, and skin tests are inconsistent; therefore sulphite sensitivity is best diagnosed with an oral double-blind graded challenge of ingestion of metabisulfite from 5 mg to 200 mg.<sup>29</sup> In non-asthmatic subjects, adverse reactions to sulphating agents appear to be

exceedingly rare.<sup>30</sup> Gall *et al.*<sup>4</sup> found 5 patients with positive skin test results to metabisulfite and suspected reaction to LA containing metabisulfite. When challenged all 5 tested negative.

Although subcutaneous administration of sulphites could theoretically provoke asthma in asthmatic individuals, no convincing evidence for this has appeared, although epinephrine contained in the LA may overwhelm the bronchoconstricting effects of sulphites.

Equally the theory of asthma exacerbation in asthmatic subjects has not been supported by the evidence in the form of positive metabisulfite challenge.<sup>31,32</sup> Only one immediate-type reaction is well documented in the literature, where a positive parenteral provocation test to metabisulfite was observed.<sup>33</sup> Other reports of suspected reaction to metabisulfite contained in LAs were not confirmed by reintroduction of the suspected LA or a graded challenge.<sup>34,35</sup>

### Myth 7. When allergic reaction to LA is suspected it is best to challenge the patient with another LA, preferably from a different class.

Diagnostic challenge is best done with the same drug the patient appears to have reacted to, including any additives the drug may have contained. Several protocols of incremental subcutaneous injections have been described. Challenges should be performed under close medical supervision in a specialist allergy centre, after informed consent has been signed and any contraindications taken into careful consideration. The initial dose is tailored according to the severity of the previous reaction. It may vary from 0.01 mg to 1 mg. This is followed by half-hourly incremental subcutaneous injections to the therapeutic dose of 10 or 20 mg.<sup>36,37</sup> Using LA alone avoids the question of possible reaction to additives, whereas using a non-suspected LA from the same or from a different class would answer the question of tolerance to the intended LA but gives no clarification as to the diagnosis of the index drug. This latter approach lends weight to the possibility of an LA allergy that may not in fact exist.

### Fact 5. An adverse reaction to LA may occur as a result of epinephrine.

Most LAs, with the exception of cocaine, cause dilatation of blood vessels. Addition of vasoconstrictor diminishes local blood flow, slows the rate of absorption of LA, decreases the serum peak and prolongs local effect of LA. However adding epinephrine introduces its own risk of side-effects. Adverse reactions to epinephrine include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, and hypertension, which may wrongly be diagnosed as hypersensitivity.

The type of injection including high pressure, speed, concentration of epinephrine and density of local vessels, all conditions met in dental surgery, increases the risk of accidental vascular injection and toxic effect. In the dental surgery the concentration of epinephrine in an LA cartridge is 12.5 mg/ml. It is 2.5 times more concentrated than in a vial for subcutaneous injection and it may, in part, explain the excess of referrals for LA adverse reactions during dental care.

### Fact 6. Toxic effect of LA may occasionally be misdiagnosed as LA allergy.

Toxic adverse reactions associated with LA relate either to systemic exposure or local pharmacological effect. Peripheral toxicity may elicit transient or permanent neurological deficit. Systemic exposure to exces-

sive quantities results in central nervous system and cardiovascular effects. It is worth noting that nervous system effects occur at lower blood plasma concentrations. These initially include a feeling of inebriation and light-headedness followed by sedation, circumoral paraesthesia and twitching, tinnitus, tremor, dizziness, blurred vision, and seizures followed by depression. With increasingly greater exposure, drowsiness, loss of consciousness, respiratory depression and apnoea may follow; convulsions may occur in severe reactions. On intravenous injection, convulsions and cardiovascular collapse may occur very rapidly. Cardiovascular effects include hypotension, bradycardia, arrhythmias, and/or cardiac arrest.<sup>38</sup>

Most of the reactions, however, are vasovagal and related to the stress and the pain of the injection. It is therefore hardly surprising that when these reactions were investigated as many as 7% of Norwegian high school students experienced fainting during medical injections and 2% during dental injections.<sup>39</sup> In addition other subjective reactions are likely to occur, which are usually not reproducible by challenge.

## CONCLUSION

Delayed sensitisation occurs mainly with ester-LAs, eliciting either contact dermatitis when used topically or delayed oedema when injected. These types of reactions are proven by patch testing read at 24 hours and 48 hours. Immediate adverse reactions to amide-LAs are frequently suspected but are most commonly subjective reactions or vasovagal reflexes related to stress and pain. Toxic effect may occur with epinephrine or LA molecules. Allergic hypersensitivity to amide-LAs, metabisulfite or paraben appears to be exceptional. Immediate allergic skin tests have low sensitivity and low specificity. A negative skin test result does not rule out LA allergy and a positive skin test result does not confirm it. Therefore the correct diagnosis can only be established by incremental subcutaneous reintroduction of LA during carefully conducted and monitored challenges.

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