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Allergy skin testing with nonirritating concentrations of anesthetic agents

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ABSTRACT

Immediate hypersensitivity reactions to anesthetic agents are rare, but with a worrying morbidity and mortality rate. Allergy evaluation is mandatory when hypersensitivity reactions to anaesthetic agents are suspected. Skin prick tests and intradermal tests are important tools due to their clinical utility in establishing the diagnosis of IgE-mediated hypersensitivity and evaluation of cross-reactivity. This article presents, for informational purposes only, the nonirritating concentrations of general anesthetics and adjuvant agents, neuromuscular blocking agents and agents used in local and regional anesthesia, used in clinical practice for allergy skin testing according to international guidelines. The delayed hypersensitivity adverse reactions can be assessed by patch testing. Concentrations used for such skin testing with topical anesthetic agents from the European baseline series, international comprehensive baseline series and medicament series, are also presented.

Keywords: anaesthetics, allergy skin tests, drug concentrations

INTRODUCTION

Even if hypersensitivity reactions to anesthetic agents are rare, they should be assessed properly. These may be immediate allergic adverse reactions, especially to agents used in general, regional or local anesthesia, usually evaluated by skin prick testing (SPT) and intradermal testing (IDT), or delayed hypersensitivity adverse reactions, mainly to topical anesthetics, generally assessed by patch testing.

IMMEDIATE-TYPE HYPERSENSITIVITY ADVERSE REACTIONS TO ANAESTHETIC AGENTS

A worrying risk of morbidity and mortality may be associated with anesthetics in the perioperative setting [1,2]. The incidence of perioperative anaphylaxis was estimated to be about 1 in 10,000 anesthetic procedures [3]. Allergy assessment of immediate perioperative hypersensitivity adverse reactions includes SPT and IDT with barbiturate and nonbarbiturate intravenous general anesthetics, benzodiazepine sedative-anesthetic medication, opioid analgesic drugs, neuromuscular blocking agents and reversal agents, along with serum tryptase levels, serum specific IgE immunoassays, and, if appropriate/possible, drug provocation tests [4-6]. In usual clinical practice, the key allergy tests for immediate hypersensitivity to anesthetics and adjuvant agents are SPT and IDT. To limit the false-negative results, the moment for such *in vivo* tests is between four weeks to four months after the reaction. SPT is recommended to be performed first, and, if the results for the tested drugs are negative, IDT will be done subsequently. If a SPT is undoubtedly positive, IDT should be avoided. If the perioperative reactions are severe, international guidelines recommend starting the skin tests with

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lower concentrations. Using 2-3 additional ten-fold dilutions of the maximum nonirritating concentrations, gradually increasing up to these levels, is a similar approach to antibiotic allergy skin testing [6-15]. Hypersensitivity reactions related to general anesthesia may be also due to other factors unrelated to anesthetics (beyond the scope of this article), such as sentinel node dyes (methylene blue, patent blue V and its derivative isosulfan blue), colloid plasma expanders (succinylated gelatin solution for intravenous infusion), other agents used in cardiac surgery (aprotinin, protamine), antiseptics (chlorhexidine, povidone iodine), and latex [15].

ALLERGY SKIN TESTING WITH GENERAL ANAESTHETICS AND ADJUVANT AGENTS

General anesthesia is an important medical procedure to tolerate specific surgical interventions. Thus, patients receive medications to achieve a controlled, reversible state of unconsciousness, analgesia and amnesia, with or without reversible muscle paralysis. Halogenated general anesthetics administered by inhalation are either fluorinated methylethyl-ethers, such as desflurane and isoflurane, or sevoflurane, a poly-fluorinated isopropyl-methyl-ether, with no reported cases of IgE-mediated allergic reactions to these volatile anesthetics so far [15].

IgE-mediated allergy to intravenous general anesthetics is rare. Agents used for SPT and IDT (Table 1) include nonbarbiturate intravenous general anesthetics (propofol, etomidate and ketamine), barbiturate intravenous general anesthetic (thiopental) and benzodiazepine sedative-anesthetic (midazolam) agents, in established nonirritating concentrations.

TABLE 1. Intravenous general anesthetic agents and suggested maximum nonirritating concentrations for allergy skin testing SPT and IDT, adapted from European and American guidelines [6,15]

Class/drugs	Maximum nonirritative concentrations	
	SPT	IDT
Nonbarbiturate intravenous general anesthetics		
propofol	10 mg/mL	1 mg/mL
etomidate	2 mg/mL	0.2 mg/mL
ketamine	10 mg/mL	0.1 mg/mL
Barbiturate intravenous general anesthetic		
thiopental	25 mg/mL	2.5 mg/mL
Benzodiazepine sedative-anesthetic agent		
midazolam	5 mg/mL	0.05 mg/mL

Propofol is a nonbarbiturate general anesthetic widely used as an intravenous sedative-hypnotic agent for the induction and maintenance of anesthesia or for sedation. This alkylphenol derivative (2,6-di-isopropylphenol) is marketed as an oil-in-water emulsion, using purified egg lecithin as excipient and refined soybean oil as an emulsifying agent. The extremely rare documented propofol-induced IgE-mediated hypersensitivity reactions are elicited by the isopropyl or phenol groups rather than the lipid vehicle components. Although there have been concerns in the past regarding its use in egg and soybean allergic patients, it is now considered not necessary to avoid this anesthetic in case of egg, soy or peanut allergy. Propofol may also stimulate directly mast cell histamine release, especially in young patients [6,9,14,15]. Since hypnotics do not present cross-reactivity, allergy tests are important in finding an alternative agent. According to the latest European, American and Australian guidelines, the nonirritating concentrations of propofol are 10 mg/mL for SPT and 1 mg/mL for IDT [6,12,15]. To obtain these concentrations, if an infusion vial with propofol 10 mg/mL is available, an undiluted concentration will be used for SPT, and a further additional 1:10 dilution with sterile sodium chloride 0.9% will be used for IDT [13].

Etomidate, a nonbarbiturate general anesthetic without analgesic activity, is a carboxylated derivative of imidazole with pharmacological properties similar to benzodiazepines and barbiturates. It is indicated for administration by intravenous injection for the induction of general anesthesia and may be used as an additional agent during the maintenance of anesthesia for short operative procedures. Similar to propofol, the injectable emulsion of etomidate has purified egg lecithin and refined soybean oil as excipients, without significant safety consequences. Allergic reactions to etomidate appear to be extremely rare. For SPT and IDT, the nonirritating concentration of etomidate is 2 mg/mL and 0.2 mg/mL, respectively [6,9,10,15]. In clinical practice, for instance, if a 10 mL vial with 20 mg etomidate is available (2 mg/mL), an undiluted concentration will be used for SPT, and the IDT will be performed with a further 1:10 dilution of it, using isotonic sodium chloride solution for infusion [13].

Ketamine, a phenyl-methylamino-cyclohexanone synthetic derivative, is a unique nonbarbiturate phencyclidine intravenous general anesthetic drug. This hydrosoluble aryl-cyclo-alkylamine is among the most important general anesthetics that has been globally in clinical practice for many years. Ketamine is primarily used for the induction and maintenance of general anesthesia and has a marked analgesic action. As in the case of etomidate, hypersensitivity reactions to this anesthetic agent are considered extremely rare, with no IgE-mediated allergic mechanisms recognized up to now. Since ketamine is commercially available in Romania, only

as a 50 mg/mL injectable solution, we suggest a nonirritating concentration of 10 mg/mL for SPT according to American guidelines, and 0.1 mg/mL for IDT according to European and Australian guidelines [6,9,12,15,16]. To provide these concentrations for skin testing, 2 mL (or 0.2 mL) are extracted from an available 10 mL vial containing ketamine base 500 mg as an injectable solution (50 mg/mL), and 8 mL (or 0.8 mL) isotonic sodium chloride is added to obtain 10 mg/mL as concentration for SPT, thereafter an additional 1:100 dilution is proposed as concentration for IDT [13].

Esketamine, the *S*-enantiomer of racemic ketamine, is usually marketed in European countries as a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist administered via a nasal spray device indicated, in conjunction with an oral antidepressant, for the management of treatment-resistant depression in adults. In some countries, such as France, but not in Romania, esketamine is also used to initiate and perform general anesthesia. The maximum nonirritating concentrations suggested by the European guidelines are 25 mg/mL for SPT and 0.25 mg/mL for IDT [6]. These can be achieved using the undiluted solution from a 2 mL ampoule with 50 mg esketamine (or a 10 mL ampoule with 250 mg) for SPT and a 1:100 dilution for IDT.

Thiopental sodium, also known as thiopentone, is an ethyl-methylbutyl thiobarbiturate derivative used intravenously as a rapid-onset ultrashort-acting general anesthetic agent that induces hypnosis and anesthesia, but not analgesia. Allergic reactions to barbiturates are now rare, due to their decreased use. IgE-mediated hypersensitivity reactions are still mentioned, although thiopental is less currently used. It should also be noted that most adverse reactions are induced by non-specific mast cell degranulation [9-11]. According to the latest European and Australian guidelines, the nonirritating concentrations of thiopental are 25 mg/mL for SPT and 2.5 mg/mL for IDT [6,12]. For example, if a vial with 500 mg thiopental powder is available, by adding 20 mL sodium chloride 0.9% a solution containing thiopental 25 mg/mL is obtained to be used for SPT, and then further perform a 1:10 dilution in order to obtain the concentration of 2.5 mg/mL for IDT [13].

Midazolam is a short-acting hydrosoluble benzodiazepine indicated intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia, as an intravenous agent for induction of general anesthesia (before administration of other anesthetic agents) and for sedation/anxiolysis/amnesia prior to or during various diagnostic or therapeutic procedures. It is also used as a continuous intravenous infusion for sedation of intubated and mechanically ventilated patients. Despite its widespread use, IgE-mediated allergic hypersensitivity reactions to midazolam are extremely rare [9,17,18]. The midazolam's highest nonirritating concentrations according to European guidelines has been reported as 5 mg/mL for SPT and 0.05 mg/mL for IDT [6,12,15]. For example, if a 1 mL ampoule with 5 mg midazolam (as hydrochloride) is available, the undiluted concentration (5 mg/mL) is used for SPT, while for IDT a subsequent 1:100 dilution is needed [6].

Regarding **opioid analgesics** used in general anesthesia it is important to mention that only a few cases of immediate allergy to fentanyl have been reported. No IgE-mediated hypersensitivity reactions have been declared for alfentanil, remifentanil, and sufentanil, but anaphylaxis was reported for pethidine. Maximum nonirritating concentrations for skin testing are presented in Table 2. These opioids have no significant local effect on mast cells [6,15].

TABLE 2. Anilidopiperidine opioid analgesics used in general anesthesia and their maximum nonirritating concentrations for allergy skin testing SPT and IDT, according to European and American guidelines [6,15]

Opioid drugs	Maximum nonirritative concentrations	
	SPT	IDT
fentanyl	0.05 mg/mL	0.005 mg/mL
alfentanil	0.5 mg/mL	0.05 mg/mL
sufentanil	0.005 mg/mL	0.0005 mg/mL
remifentanil	0.05 mg/mL	0.005 mg/mL

Fentanyl is a synthetic rapid-acting opioid agonist acting as a strong analgesic agent. By having a 4-anilidopiperidine structure, it binds to the mu-opioid receptors thus being a drug that alleviates pain during induction, maintenance, and recovery from general or regional anesthesia [9]. Reactions to fentanyl are rare, with few publications on suspected IgE-mediated allergic hypersensitivity to this opioid [19,20]. According to international guidelines, the maximum nonirritating concentrations of fentanyl are 0.05 mg/mL for SPT and 0.005 mg/mL for IDT [6,12,15]. For example, if a 2 mL ampoule with 0.05 mg/mL (50 μg/mL) of fentanyl (as citrate) is available, SPT will be done without any dilution (full-strength), while IDT will be performed with a 1:10 dilution using sodium chloride solution for infusion [13].

Remifentanil is a synthetic opioid agonist from the same anilidopiperidine group, with an ultra-short duration of action, used during the induction and maintenance of general anesthesia [9]. The nonirritating concentrations for skin testing with remifentanil are the same as those for fentanyl [6, 12,15]. If a vial containing 1 mg remifentanil hydrochloride powder is available, after adding 1 mL sodium chloride 0.9 % solution for injection a concentration of 1 mg/mL is obtained, afterwards, a 1:2

dilution followed by a 1:10 dilution should be performed in order to obtain the concentration for SPT. For IDT, an additional 1:10 dilution of the SPT solution is necessary [13].

Sufentanil is a thienyl derivative of fentanyl. Nowadays, this 4-anilidopiperidine is the most potent opioid in clinical practice, 10 times more potent than fentanyl [9]. The maximum nonirritating concentration of sufentanil is 0.005 mg/mL for SPT and 0.0005 mg/mL for IDT [6,15]. For example, if an ampoule with sufentanil citrate 0.005 mg/mL solution is available, an undiluted concentration may be used for SPT and an additional 1:10 dilution for IDT [13].

Alfentanil is another opioid agonist of the 4-anilidopiperidine series with a short-acting duration of action, used for induction and maintenance of general anesthesia, and postoperative pain [9]. It is not available in Romania [13]. The nonirritating concentration is 0.5 mg/mL for SPT and 0.05 mg/mL for IDT [6,12,15]. For example, with a 500 µg vial of alfentanil, SPT will be performed without any dilution, and IDT will be performed with a further 1:10 dilution [21].

Pethidine, also known as meperidine, is a synthetic 4-phenyl-piperidine opioid agonist with a similar mechanism of action as morphine. This adjunct to preoperative medication acts as an agonist to the *mu*-opioid receptor, but also it stimulates the *kappa*-opioid receptors having an anti-shivering effect. Like morphine, pethidine induces potent non-specific release of histamine. According to Australian guidelines, the nonirritating concentration of pethidine is 25 mg/mL for SPT and 0.0025 mg/mL for IDT. For example, if a 2 mL vial with 100 mg pethidine is available (50 mg/mL), SPT will be performed with a 1:2 dilution. Subsequently, in order to obtain the IDT concentration, a dilution of 1:10,000 (10^{-4}) will be required [9,12,21,26].

Unlike the above-mentioned drugs, **morphine** is a natural opioid agonist with a structure of phenanthrene derivative used for the management of moderate to severe pain [9]. It is known that for morphine, direct mast cell degranulation through the MRGPRX2 receptor is much more prevalent than IgE-mediated hypersensitivity [22,23]. Morphine cross-reacts to codeine, with no evidence of cross-reactivity between different opioid subclasses. Some patients with allergy to neuromuscular blocking agents present specific IgE to morphine, a biomarker for antibodies against the quaternary ammonium component, therefore this should not be assessed as hypersensitivity to morphine [6,12,24,25]. Morphine is a tertiary amine that, if insufficiently diluted, causes nonspecific direct histamine release generating false-positive skin testing results. The nonirritating concentration of morphine is 1 mg/mL for SPT and 0.005 mg/mL for IDT according to European guidelines. The Australian guidelines suggest an even lower concentration of 0.0001 mg/mL for IDT [6,12]. In practice, if a 1 mL glass ampoule with 20 mg morphine hydrochloride (20 mg/mL) is available, a 1:2 dilution is performed followed by a further 1:10 dilution for SPT. Many subsequent dilutions are done thereafter in order to obtain the nonirritating IDT concentrations [13].

ALLERGY SKIN TESTING WITH NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents (NMBAs) are indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. They are among the main causes of IgE-mediated and non-allergic reactions during general anesthesia or in the postoperative setting. NMBAs have been reported as the most common cause of perioperative anaphylaxis in Australia and France (approximately 60%) and the second cause, after antibiotics, in the US and UK [3,6,12,27-29]. A higher risk of anaphylaxis was associated with succinylcholine followed by rocuronium, vecuronium, pancuronium and atracurium. The quaternary ammonium NMBAs include the depolarizing neuromuscular blocker succinylcholine and the nondepolarizing neuromuscular blocking agents belonging to the benzylisoquinolinium-type, such as atracurium, cisatracurium, and mivacurium, or to the aminosteroid-type, such as pancuronium, rocuronium, and vecuronium (Table 3). IgE sensitization to NMBAs and cross-reactivities can be related to the presence of ubiquitous epitopes such as substituted quaternary ammonium groups in other classes of pharmaceuticals (such as neostigmine and pholcodine), cosmetics (tioglycol ammonium), nasal or eyedrop preservatives (benzalkonium chloride), disinfectants and industrial materials [18,27]. Hypersensitivity reactions to NMBA may be either IgE or non-IgE mediated in their pathogenesis. Allergy skin testing with NMBAs is considered to be highly sensitive (>95%) and specific (96-98%), and therefore essential for the diagnosis of IgE-mediated adverse reactions and for assessing cross-reactivity [10,18]. SPT and IDT do not evaluate or do not exclude non-IgE-mediated hypersensitivity adverse reactions, of different severities, or other non-allergic adverse reactions.

Succinylcholine (suxamethonium) is a quaternary ammonium ion, a bis-choline ester of succinic acid, used as a depolarizing skeletal muscle relaxant [9]. In a recent UK national audit project (NAP6), the most frequent clinical feature of anaphylaxis caused by succinylcholine was bronchospasm, particularly associated with the female gender and morbid obe-

TABLE 3. Quaternary ammonium neuromuscular blocking agents (NMBAs) used in general anaesthesia and their maximum nonirritating concentrations for allergy skin testing SPT and IDT, according to European guidelines [6]

Class/drugs	Maximum nonirritative concentrations	
	SPT	IDT
Succinylcholine as depolarizing NMBA		
suxamethonium	10 mg/mL	0.1 mg/mL
Benzylisoquinolinium-type nondepolarizing NMBAs		
atracurium	1 mg/mL	0.01 mg/mL
cisatracurium	2 mg/mL	0.02 mg/mL
mivacurium	0.2 mg/mL	0.002 mg/mL
Aminosteroid-type nondepolarizing NMBAs		
rocuronium	10 mg/mL	0.05 mg/mL
pancuronium	2 mg/mL	0.02 mg/mL
vecuronium	4 mg/mL	0.04 mg/mL

sity [3]. The maximum nonirritating concentration of succinylcholine for SPT is 10 mg/mL and for IDT is 0.1 mg/mL [6,12,15]. For example, if a 5 mL vial containing suxamethonium chloride 100 mg in solution is available (20 mg/mL), SPT will be performed with a 1:2 dilution, and IDT will be completed using an additional 1:100 dilution of the mentioned SPT maximal nonirritating concentration [13].

Atracurium is a quaternary ammonium compound used as a nondepolarizing neuromuscular blocking agent belonging to the benzylisoquinoline family and acting like a competitive acetylcholine antagonist [9]. In the NAP6, the most frequent clinical feature of anaphylaxis caused by atracurium was hypotension, and it was more present in men [3]. The maximum nonirritating concentration of atracurium for SPT is 1 mg/mL and for IDT is 0.01 mg/mL [6,12,15]. To exemplify, if a 5 mL ampoule with 50 mg atracurium besylate is available (10 mg/mL), SPT will be performed with a maximum 1:10 dilution, and IDT will be made from the SPT concentration with an additional 1:100 dilution [13]. Cisatracurium, the 1*R*-cis 1'*R*-cis isomer of atracurium, is a non-depolarizing neuromuscular blocking agent from the same benzylisoquinolinium type [9]. It may be preferred as an alternative to patients who had previously anaphylaxis-type reactions to rocuronium or vecuronium [18,30,31]. The maximum nonirritating concentrations are 2 mg/mL for SPT and 0.02 mg/mL for IDT [6,12,15]. For example, if a vial with cisatracurium besylate 2 mg/mL solution for injection is available, SPT will be done with an undiluted concentration, while IDT will be performed with an additional 1:100 dilution [21].

Mivacurium is another quaternary ammonium compound used as a nondepolarizing neuromuscular blocking agent from the benzylisoquinolinium-type group [9]. Mivacurium, as well as atracurium, should be used with caution in patients with mast cell clonal disorders because of their marked histamine-releasing effect [32]. The nonirritating concentration of mivacurium for SPT and IDT is 0.2 mg/mL and 0.002 mg/mL, respectively [6,15]. In clinical practice, if a 10 mL vial with 20 mg mivacurium chloride is available (2 mg/mL), a 1:10 dilution will be used for SPT, and an additional 1:100 dilution of the SPT concentration will be used for IDT [13].

Rocuronium, an intermediate-acting mono-quaternary ammonium steroid, is a nondepolarizing neuromuscular blocker [9]. It is one of the most frequent NMBAs involved in perioperative anaphylaxis by itself or by the formation of a sugammadex-rocuronium complex [33-35]. The rocuronium's highest nonirritating concentration has been reported as 10 mg/mL for SPT and 0.05 mg/mL for IDT [6,12,15]. In clinical practice, from a vial of 10 mg/mL rocuronium bromide, the undiluted concentration (1:1) will be used for SPT, and a 1:200 dilution will be used for IDT according to American and European guidelines [13].

Vecuronium is another synthetic, intermediate-acting, mono-quaternary ammonium steroid used as a nondepolarizing neuromuscular blocking agent [9]. The European guidelines have reported the vecuronium's highest nonirritating concentration as 4 mg/mL for SPT and 0.04 mg/mL for IDT. For example, if a vial with 10 mg of vecuronium bromide as very fine microscopic crystalline particles is available, the SPT concentration may be obtained by adding 1.5 mL sodium chloride 0.9% to 10 mg vecuronium bromide in 1 mL solution, subsequently, a further 1:100 dilution of this concentration may be used for IDT [6,21]. Pancuronium is a synthetic, long-acting bis-quaternary ammonium steroid acting also as a nondepolarizing curare-mimetic muscle relaxant [9]. The maximum nonirritating concentration of pancuronium is 2 mg/mL for SPT and 0.02 mg/mL for IDT [6,15]. To exemplify, if an ampoule containing 4 mg/2 mL of pancuronium bromide (2 mg/mL) is available, SPT will be performed with the undiluted concentration, and IDT will be made with a 1:100 dilution according to the latest European guidelines [2,21]. These two last-mentioned aminosteroid-type NMBAs are not currently available in Romania [13].

Although not the topic of this paper, it is important to mention in this section the agents for the reversal of neuromuscular blockade, commonly represented by neostigmine, an anticholinesterase, and sugammadex, a cyclodextrin reversal agent for aminosteroids. Nonirritative concentrations for **neostigmine** methylsulfate are 0.5 mg/mL for SPT and 0.025 mg/mL (1:20) for IDT, adapted from Australian recommendations [12,13], while for **sugammadex**, these are 100 mg/mL for SPT and 10 mg/mL (1:10) for IDT, according to European guidelines [6]. Moreover, **atropine** sulfate for injection is indicated for tempo-

rary blockade of severe or life-threatening muscarinic effects, and it is used as an antisialagogue and anti-vagal agent, and to treat bradyasystolic cardiac arrest. SPT, as part of perioperative hypersensitivity assessment, may be performed using undiluted atropine sulfate 1 mg/mL [15] or a concentration of 0.6 mg/mL [12,15], while IDT will be completed using a further 1:1000 dilution [12].

ALLERGY SKIN TESTING WITH AGENTS USED IN LOCAL AND REGIONAL ANAESTHESIA

Local anesthetics are divided into two subgroups (amino amide-type and benzoic ester-type). Amide anesthetics are mainly indicated for local or regional analgesia and anesthesia by local infiltration, peripheral nerve block techniques, and central neural techniques, including epidural and caudal blocks. The worrying frequency of adverse events related to local, infiltrative, or conductive anesthesia in both simple and complex dental procedures is due to vasovagal reactions, dose-related toxic effects and side effects of adrenaline (epinephrine) used as vasoconstrictor additive, rather than immediate-type allergic reactions. True IgE-mediated allergic reactions to the amide-type local anesthetics are extremely rare relative to their extensive use and are usually confirmed by SPT (full-strength) or IDT (1:10 dilution). With a sensitivity of 100% and a specificity of almost 95%, skin testing is an important tool for *in vivo* allergy diagnosis and for assessing cross-reactivity within a structural group. Instead, there is no cross-reactivity between amide- and ester-type local anesthetics. Nevertheless, the subcutaneous provocation test remains the gold standard to exclude local anesthetics allergy [36-41].

Lidocaine (lignocaine), mepivacaine and articaine are usually used as amide-type local anesthetics with a moderate duration of action for dental infiltration anesthesia. Moreover, lidocaine is being used in addition to other local and regional anesthesia procedures, and as a class 1b antiarrhythmic agent for ventricular arrhythmias especially after myocardial infarction. Interestingly, lidocaine has a similar chemical structure to tolperisone, a centrally-acting muscle relaxant known to induce anaphylaxis [13,21].

In clinical practice, local anaesthetic preparations without epinephrine (adrenaline) as a vasoconstrictor additive, and without parabens or sulfites as excipients, should be used for allergy skin testing (Table 4).

Lidocaine is a synthetic aminoethyl amide local anesthetic that is the most frequently suspected agent to induce immediate hypersensitivity reactions from the amide-type group [40-43]. The maximum nonirritating concentration of lidocaine is reported to be 10 mg/mL for SPT and 1 mg/mL for IDT [6,15]. To obtain these concentrations, if lidocaine hydrochloride 100 mg/10 mL (1%) solution for injection in an ampoule is available, the undiluted concentration (full-strength) of 10 mg/mL lidocaine will be used for SPT, and an additional 1:10 dilution will be performed for IDT [13].

TABLE 4. Local anaesthetics and their maximum nonirritating concentrations for allergy skin testing SPT and IDT, according to European guidelines [6]

Amide-type anaesthetics	Maximum nonirritative concentrations	
	SPT	IDT
lidocaine (without adrenaline)	10 mg/mL	1 mg/mL
mepivacaine (without adrenaline)	20 mg/mL	2 mg/mL
articaine (without adrenaline)	20 mg/mL	2 mg/mL
bupivacaine	2.5 mg/mL	0.25 mg/mL
levobupivacaine	7.5 mg/mL	0.75 mg/mL
ropivacaine	10 mg/mL	1 mg/mL

Mepivacaine is a piperidine carboxamide local anesthetic having maximum nonirritating concentrations of 20 mg/mL for SPT and 2 mg/mL for IDT [6, 9,15]. To exemplify, if a cartridge containing 30 mg/mL mepivacaine hydrochloride solution for injection is available, in order to obtain the concentration for SPT, 0.5 mL of sterile 0.9% saline solution is added to 1 mL of the 30 mg/mL mepivacaine solution (or 0.1 mL saline added to 0.2 mL full-strength anaesthetic solution). Afterward, to obtain the IDT concentration, an additional 1:10 dilution should be performed from the SPT maximum nonirritating solution mentioned [13].

Articaine is an amide-type local anesthetic with a thiophene ring structure used for dental anesthetic procedures, sometimes used as an option in patients with lidocaine hypersensitivity. The maximum nonirritating concentrations of articaine are 20 mg/mL for SPT and 2 mg/mL for IDT. A practical problem with articaine skin testing is that in some European countries, such as Romania, all commercial available preparations with articaine contain epinephrine (adrenaline) as vasoconstrictor, and are not suitable for allergy skin testing. In other countries, such as Germany, cartridges with articaine hydrochloride 40 mg/mL solution without adrenaline are available, and in this case, SPT will be performed with a 1:2 dilution, while IDT will be performed with a further 1:10 dilution in accordance with European guidelines [6,13,44].

Bupivacaine, levobupivacaine, ropivacaine and prilocaine are amide-type local anesthetic agents indicated usually as subarachnoid injection for the production of subarachnoid block (spinal anesthesia) [13,21].

Bupivacaine is an amide-type, long-acting local anesthetic with analgesic effects and a longer duration of action than other local anesthetics [9]. It is

indicated for subarachnoid injection for the production of subarachnoid block (spinal anesthesia). The maximum nonirritating concentration of bupivacaine for SPT is 2.5 mg/mL and for IDT is 0.25 mg/mL [6,15]. To obtain these concentrations, if a bupivacaine hydrochloride monohydrate 5 mg/mL (0.5%) solution for injection in an ampoule is available, a dilution of 1:2 obtained from it will be used for SPT, and an additional 1:10 dilution from the SPT concentration will be used for IDT [13].

Levobupivacaine is the *S*-enantiomer of bupivacaine used in some countries for local or regional anesthesia. This anesthetic can cause extremely rare immediate hypersensitivity reactions [42]. The maximum nonirritating concentration of levobupivacaine for SPT is 7.5 mg/mL and for IDT is 0.75 mg/mL [6]. If an Italian anesthetic product with levobupivacaine 7.5 mg/mL is available, this full-strength concentration will be used for SPT, and an additional dilution of 1:10 will be used for IDT according to European guidelines [21].

Ropivacaine is a piperidine carboxamide-based amide-type local anesthetic associated extremely rare with immediate hypersensitivity reactions [42]. It is indicated for surgical anaesthesia (epidural block, major nerve block and local infiltration) and for acute pain management (epidural continuous infusion or intermittent bolus and local infiltration). Maximum nonirritating concentrations of ropivacaine for SPT are mentioned as 2 mg/mL in American guidelines and 10 mg/mL in the European and Australian ones. For IDT 1:10 dilutions from these concentrations are recommended by the European and American guidelines, and 1:100 respectively by the Australian ones [6,12,13,15]. Vials with 2 mg or 10 mg ropivacaine hydrochloride per mL may be used to obtain these concentrations for skin testing [13].

Prilocaine is a toluidine-based amide-type local anesthetic used for spinal anaesthesia in some countries including UK, but not in Romania. The nonirritating concentration of prilocaine is 20 mg/mL for SPT and 2 mg/mL for IDT. For example, if an ampoule with 5 mL solution containing 100 mg of prilocaine hydrochloride is available, SPT will be done with the undiluted concentration, and IDT with a 1:10 dilution according to European guidelines [6,21]. An ester-type local anesthetic used for regional anaesthesia in some countries, not in Romania, is chloroprocaine, for which SPT may be performed with a 10 mg/mL concentration, while IDT with a 1:10 dilution, respectively 1 mg/mL [6,13].

As a corollary, we underline that although immediate allergic reactions to anaesthetics are rare, an allergy workup with skin testing using drugs for anaesthesia is important in clinical practice in Romania, as epidemiological data from our country reveal that NMBAs are important culprit agents [45-47]. SPT and IDT with anesthetic agents are the most common methods for identifying IgE involvement in such adverse drug reactions. A crucial approach of these allergy tests is that drug concentrations used must be nonirritating and low enough not to activate directly the mast cell receptors called Mas-related G protein coupled receptors X2 (MRGPRX2), but sufficient to trigger IgE reactions generated by the interaction of the drug epitopes with the specific IgE antibodies bound to the high-affinity IgE receptors on the surface of cutaneous mast cells [48]. *In vivo* skin testing is recommended to be performed 1-4 months post-event and at least 4-6 weeks post-event to avoid false-negative results, while any drugs with H1 antihistamine effect should be stopped at least five days prior. Histamine dihydrochloride 10 mg/mL as positive SPT control and sodium chloride 0.9% as IDT and SPT negative controls should always be used. SPT and IDT are performed on the volar side of the forearms (or on the back), at all times using commercially available anesthetic drugs. The stability details regarding different agents used in the perioperative setting must be considered. Skin testing results are assessed after 20 min, and a wheal with an increase in diameter of ≥ 3 mm versus the original one (together with a flare) is considered a positive result. Obtaining detailed information about the patient's medical history, current medications, history of hypersensitivity to drugs and perioperative exposure to drugs related to the event is of paramount importance, therefore collaboration between anaesthesiologists and allergists is critical. Because the risk of anaphylaxis during skin testing exists, even if it is very low, such an *in vivo* allergy workup should be performed in appropriate settings by specialists with experience in perioperative hypersensitivity investigation [6,7,45-47].

DELAYED-TYPE HYPERSENSITIVITY ADVERSE REACTIONS

Such adverse reactions account for a great part of allergic reactions to local anesthetics. They are more common with the use of topical anesthetics and may occur with the ester-type representatives, but also with the amide-type ones. Contact allergy can be suspected by dermatologists and allergists, and should be diagnosed by skin patch testing, which is different from skin allergy testing represented by SPT and IDT. Application of patch test haptens or contact allergens on the back is recommended for practical reasons, but the outer surface of the upper arms can also be considered. With regard to high sensitivity, a 48 h occlusion time is recommended, with an usual reading at 72 h (day 3), and a late reading at around day 7. Positive patch test reactions, reported at day 3, or at a later reading time, as

weak positive (+) with erythema, infiltration, possibly papules, strong positive (++) with erythema, infiltration, papules and vesicles or extreme positive (+++) with intense erythema, infiltrate and coalescing vesicles, are usually assessed as allergic. Some authors discuss very late readings on day 15 which may reveal positive reactions that had not observed at previous readings, with *para* group allergens, including *p*-phenylenediamine (PPD) and benzocaine (ethyl *p*-aminobenzoate) being of particular concern. By knowing the anesthetic hapten involved in contact hypersensitivity, the patient can avoid the occurrence of allergic contact dermatitis [50-53].

Local anesthetics of the *p*-aminobenzoic acid derivatives group or ester-type used for patch testing are: benzocaine, amylocaine, procaine, tetracaine (amethocaine). These are thought to have strong sensitizing potential, but are less used nowadays. Benzocaine is still used in some hemorrhoidal products (ointments and suppositories) and lozenges with chlorhexidine dihydrochloride for stomatitis and gingivitis. Topical medicinal products containing benzocaine are available in some countries for treating UVB-light induced sunburn pain, but local anesthetic creams are actually avoided for the treatment of sunburns due to the risk of skin irritation or contact allergy. In clinical practice, benzocaine is a common sensitizer in patients presenting exclusively with anogenital dermatitis. Cross-reactivity may be detected among ester-type anesthetics. Benzocaine, may also cross-react with many other *para*-group haptens: *p*-phenylenediamine (PPD) and other precursors or primary intermediates in oxidative hair dyes, such as toluene-2,5-diamine sulfate (TDS) or *p*-aminophenol (PAP) in permanent and demi-permanent dyes; *N*-isopropyl-*N*'-phenyl-p-phenylenediamine (IPPD) used as black rubber antioxidant; azo textile dye Dispersion Orange 3 (DO3) used for dyeing synthetic fibers such as triacetate, nylon or polyester; derivatives of *p*-aminobenzoic acid (PABA) used as UVB chemical filters in photoprotection products, such as ethylhexyl(octyl)-dimethyl PABA and ethylhexyl(octyl) triazone. Cross-reactivity of benzocaine with these contact allergens may require avoidance. Cross-reactions have been also described with other *para* compounds, such as parabens and sulfonamides, but they are rare. In general, benzocaine-sensitive individuals can safely use amide derivatives such as lidocaine. The amino amide-type of local anesthetics include, beside lidocaine (lignocaine), dibucaine (cinchocaine) and prilocaine. A combination of lidocaine and prilocaine may be used as a cream for topical anesthesia of the skin for medical needle insertion and superficial surgical procedures, and as a sprayed cutaneous solution for primary premature ejaculation in adult men. While procaine hydrochloride was promoted in topical anti-aging product, a medicated plaster with lidocaine may still be indicated for the symptomatic relief of post-herpetic neuralgia in adults [13,21,49,50,54,55].

The concentrations as % (w/w) for local anesthetics in petrolatum (pet) used for patch testing with the European baseline series 2023 are for the caine mix III 10% pet: benzocaine 5%, tetracaine hydrochloride 2.5%, and dibucaine hydrochloride 2.5% (Table 5). It was recently agreed to use this caine mix instead of benzocaine alone, given the increased sensitivity of the mix in screening for contact sensitization to local anesthetics. In the international comprehensive baseline series, there are also individual anesthetics for patch testing, namely benzocaine 5% pet, dibucaine hydrochloride 2.5% pet and lidocaine 15% pet. Due to possible false patch negative test results, when contact allergy is strongly suspected it is still important to test to such individual haptens. Procaine hydrochloride may also be tested as 1% pet. In the Medicament Series, there is an additional caine mix IV 10% pet (lidocaine 5%, prilocaine hydrochloride 2.5%, amylocaine hydrochloride 2.5%) [13,49,56].

TABLE 5. Local anesthetics in the caine mix III and concentrations recommended for patch testing according to the European baseline series: 2023 [56]

Local anaesthetic	Concentration % in pet (petrolatum)	Concentration mg/cm^2
Caine mix III	10%	4 mg/cm^2
benzocaine	5%	2 mg/cm^2
tetracaine (amethocaine)	2.5%	1 mg/cm^2
dibucaine (cinchocaine)	2.5%	1 mg/cm^2

CONCLUSION

Physicians assessing suspected hypersensitivity reactions to anesthetic agents are advised to use their own medical judgment in accordance with the local and national guidelines, updating medical information periodically. It is very important to report such reactions to the national/regional pharmacovigilance units whenever they happen and to mention and describe the adverse events in the patient's medical documents. This article is intended only for informational purposes and does not replace the professional expertise of allergists and anesthesiologists or dermatologists. It presents the nonirritating concentrations for SPT and IDT with anesthetic agents recommended by international guidelines. These allergy skin tests do not assess and, if negative, do not exclude non-IgE-mediated immediate hypersensitivity adverse reactions, with various severities, or other non-allergic adverse reactions. Adverse reactions suspecting delayed hypersensitivity can be evaluated with patch testing.

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