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POSITION PAPER

Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper

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Abstract

Skin tests are of paramount importance for the evaluation of drug hypersensitivity reactions. Drug skin tests are often not carried out because of lack of concise information on specific test concentrations. The diagnosis of drug allergy is often based on history alone, which is an unreliable indicator of true hypersensitivity.To promote and standardize reproducible skin testing with safe and nonirritant drug concentrations in the clinical practice, the European Network and European Academy of Allergy and Clinical Immunology (EAACI) Interest Group on Drug Allergy has performed a literature search on skin test drug concentration in MEDLINE and EMBASE, reviewed and evaluated the literature in five languages using the GRADE system for quality of evidence and strength of recommendation. Where the literature is poor, we have taken into consideration the collective experience of the group.We recommend drug concentration for skin testing aiming to achieve a specificity of at least 95%. It has been possible to recommend specific drug concentration for betalactam antibiotics, perioperative drugs, heparins, platinum salts and radiocontrast media. For many other drugs, there is insufficient evidence to recommend appropriate drug concentration. There

Abbreviations
EAACI, European Academy of Allergy and Clinical Immunology; ENDA, European Network on Drug Allergy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IDT, intradermal test; Im, intramuscular; Iv, intravenous; LA, local anaesthetic; MDM, minor determinant mixture; NIHR, nonimmediate hypersensitivity reaction; NSAID, nonsteroidal anti-inflammatory drug; Sc, subcutaneous; SPT, skin prick test.

is urgent need for multicentre studies designed to establish and validate drug skin test concentration using standard protocols. For most drugs, sensitivity of skin testing is higher in immediate hypersensitivity compared to nonimmediate hypersensitivity.

Drug hypersensitivity affects about 5% of hospitalized patients and is associated with significant morbidity and mortality (1). Drug hypersensitivity reactions mediated by specific immune mechanisms are classified as drug allergy. Based on the time between drug exposure and onset of symptoms/signs, reactions may be divided into immediate and nonimmediate hypersensitivity reaction (NIHR). The mechanism underlying the former is thought to be IgE-mediated and the latter is primarily T cell-mediated. There is some overlap as early noneczematous NIHRs that become symptomatic over 1–6 h may show anaphylactic features and IgE-mediated mechanism. In drug allergy, skin testing is the most widely used method to determine sensitization, as other tests (*in vitro* or drug provocation test) are less specific, less sensitive or potentially harmful (2). There is no international consensus on how skin tests with drugs should be performed or interpreted. There have been no multicentre studies to establish drug concentration, test protocol, specificity, sensitivity and safety. Reliable skin test procedures including test concentrations for the diagnosis of drug hypersensitivity are not available for most drugs (3). Consequently, many doctors do not investigate drug reactions and rely on the history alone to make a diagnosis of drug allergy and the unjustified use/avoidance of indicated drugs.

The European Network on Drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) Interest Group on Drug Allergy have already published guidelines and position papers on procedures, such as history taking (4), general approach to skin testing (2), drug provocation tests (5), as well as recommendations for the management of betalactam hypersensitivity (6), perioperative anaphylaxis (7), radiocontrast media reactions (8), hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAID) (9) and on rapid desensitization (10).

It is the primary purpose of this paper to present skin test concentrations for practical use by the allergist. Suggested concentrations should be nonirritating aiming for the highest specificity, if possible exceeding 95%. By evaluating the literature, we developed additional key statements and recommendations concerning methodology and clinical value of skin testing for various drug classes.

Methods

Data sources

In January 2010, articles in English, German, Italian, French and Spanish with data on skin test concentrations for drugs were identified by searching the databases of MEDLINE (National Library of Medicine) and EMBASE (Elsevier Science). Keywords were the names and synonyms of the respective drugs and skin test, skin prick test (SPT), intradermal test (IDT), patch test and scratch test. Additional articles were found through archives or on the reference lists of the identified articles. Further data sources were textbooks, test concentrations recommended by national registries, existing guideline articles and experiences by members of the task force.

We restricted the search to systemically administered drugs and excluded topically applied agents causing only contact or photocontact allergy. No prospective controlled studies were found; thus, we included observational studies, case series, case reports and also the personal experience of members of the group, when other reliable data were lacking. The literature reviewed contained minimal data on testing of healthy controls.

Data extraction

Our aim has been to provide data for all widely used drugs or drug classes. Members of the task force were assigned different drug classes (Appendix 1) who retrieved identified articles and assessed the data. The relevance of articles was evaluated by the responsible authors on the basis of title and abstract. The drug classes and responsible authors are listed in Appendix 1. Selected articles were then retrieved and analysed. Detailed results of skin test concentrations for all drugs were summarized in a master table, which is available on our website http://eaaci.net/sections-a-igs/ig-on-drug-allergy/resources.html (see also Table S1 in the Supporting Information section of this paper). For drug groups where evidence was considered sufficient for recommendations to be made on skin concentrations, tables are included in the following text (Tables 1–3). In addition, for each drug or drug class, key statements on the quality of evidence and recommendation (including strength) are made. The submission of the responsible author(s) was discussed by the task force, confirmed or amended by consensus of the group.

Table 1 Nonirritating test concentrations for betalactam antibiotics

DRUG	SPT	IDT	PT
Penicilloyl-poly-L-lysine	5×10^{-5} mM	5×10^{-5} mM	NA
Minor determinant mixture	2×10^{-2} mM	2×10^{-2} mM	NA
Benzylpenicillin	10.000 UI	10.000 UI	5%
Amoxicillin	20 mg/ml	20 mg/ml	5%
Ampicillin	20 mg/ml	20 mg/ml	5%
Cephalosporins	2 mg/ml	2 mg/ml	5%

For this and all following tables: SPT, skin prick test; IDT, intradermal test; PT, patch test.

Table 2 Nonirritating test concentrations for perioperative drugs

DRUG		SPT		IDT	
Generic name	Undiluted concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)
Thiopental	25	Undiluted	25	1/10	2.5
Propofol	10	Undiluted	10	1/10	1
Ketamine	10	Undiluted	10	1/10	1
Etomidate	2	Undiluted	2	1/10	0.2
Midazolam	5	Undiluted	5	1/10	0.5
Fentanyl	0.05	Undiluted	0.05	1/10	0.005
Alfentanil	0.5	Undiluted	0.5	1/10	0.05
Sufentanil	0.005	Undiluted	0.005	1/10	0.0005
Remifentanil	0.05	Undiluted	0.05	1/10	0.005
Morphine	10	1/10	1	1/1000	0.01
Atracurium	10	1/10	1	1/1000	0.01
Cis-atracurium	2	Undiluted	2	1/100	0.02
Mivacurium*	2	1/10	0.2	1/1000	0.002
Rocuronium	10	Undiluted	10	1/200	0.05
Vecuronium†	4	Undiluted	4	1/10	0.4
Pancuronium†	2	Undiluted	2	1/10	0.2
Suxamethonium*	50	1/5	10	1/500	0.1

IDT, intradermal test; SPT, skin prick test.

*Change to increase maximum concentrations on IDT has been proposed (mivacurium 1/200 = 0.01 mg/ml and suxamethonium 1/100 = 0.5 mg/ml) ref 9, 10 from the table of the e-appendix on the website (http://eaaci.net/sections-a-igs/ig-on-drug-allergy/resources.html).

†Change to decrease maximum concentrations on IDT has been proposed (vecuronium 1/100 = 0.04 mg/ml and pancuronium 1/50 = 0.04 mg/ml) ref 9, 10 from the table of the e-appendix on the website.

Grading quality of evidence and strength of recommendation

Grading of the quality of evidence and the strength of recommendation for key statements and skin test concentrations were performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (11). Evidence was graded as high quality, if further research is very unlikely to change our confidence in the estimate of effect; moderate, if further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low, if further research is very likely to have an important impact on our confidence in the estimate of effect that is likely to change the estimate; and very low, if any estimate of effect is very uncertain. The strength of recommendation is strong, if clinicians are very certain that the benefits outweigh the risks. A recommendation is weak if the benefits and risks are finely balanced, or appreciable uncertainty exists about the magnitude of the risk. The grading of high/strong in the text denotes a high quality of evidence and strong strength of recommendation.

Results

General aspects

Skin test is the most commonly used procedure to confirm a sensitization in drug hypersensitivity; for many drugs, *in vitro* tests are not available or sufficiently validated (high/strong).

Skin prick test (SPT) and IDT with immediate readings are used for investigation of immediate hypersensitivity reactions. These tend to occur within 1 h after drug administration, but may develop after 1–6 h (and exceptionally later). Symptoms are often confined to the skin and mucous membranes, for example, generalized rash/urticaria or angioedema and may progress in some cases to more severe symptoms of bronchospasm, hypotension and anaphylactic shock. Investigations of NIHR should include IDT with late readings as well as patch tests (2). Nonimmediate hypersensitivity reactions develop within hours to days but in highly sensitized individuals may manifest within 24 h. Symptoms of NIHR show a diversity of clinical manifestations with maculopapular exanthema being the most common presentation (high/strong).

A validated protocol should be used, and guidelines have been published (high/strong) (2, 12). Scratch tests are poorly standardized and are not recommended (moderate/strong). For children, the tools used for management established in adults are applicable even though there is insufficient evidence of their suitability. A separate position paper on paediatric drug hypersensitivity is in progress.

The sensitivity of skin tests appears to be moderate to high for immediate hypersensitivity reactions to betalactam antibiotics, perioperative drugs, heparins, platinum salts, radiocontrast media, but low for many other drugs (moderate/weak).

The parenteral preparation of the suspected drug, preferably the intravenous form at the recommended concentration, should be used for SPT and IDT. For drugs suspected of

Table 3 Nonirritating test concentrations for selected other drugs and drug classes

Drug or drug class	SPT	IDT	Patch
Anticoagulants			
Heparins*	Undiluted	1/10 diluted	Undiluted
Heparinoids†	Undiluted	1/10 diluted	Undiluted
Platinum salts			
Carboplatin	10 mg/ml	1 mg/ml	NA
Oxaliplatin	1 mg/ml	0.1 mg/ml	NA
Cisplatin	1 mg/ml	0.1 mg/ml	NA
NSAIDs			
Pyrazolones‡	Powder	0.1 mg/ml	10%
Coxibs§	Powder		10%
Other NSAIDs¶	Powder	0.1 mg/ml	10%
Biologicals			
Adalimumab	50 mg/ml	50 mg/ml	Undiluted
Etanercept	25 mg/ml	5 mg/ml	NA
Infliximab	10 mg/ml	10 mg/ml	NA
Omalizumab	1.25 μg/ml	1.25 μg/ml	NA
Others			
Local anaesthetics	Undiluted	1/10 diluted	Undiluted
Iodinated contrast media	Undiluted	1/10 diluted	Undiluted
Gadolinium chélates	Undiluted	1/10 diluted	NA
Patent blue	Undiluted	1/10 diluted	NA
Methylene blue		1/100 diluted	
Fluorescein	Undiluted	1/10 diluted	Undiluted
Proton pump inhibitors**	Undiluted	40 mg/ml	10%
Anticonvulsants††	NA	NA	10%
Chlorhexidine digluconate	5 mg/ml	0.002 mg/ml	1%

IDT, intradermal test; NSAID, nonsteroidal anti-inflammatory drug; SPT, skin prick test.

*Heparins: heparin sodium, nadroparin, dalteparin and enoxaparin; testing contraindicated in HIT.

†Heparinoids: danaparoid and fondaparinux.

‡Pyrazolones: metamizol, paracetamol, propyphenazone, aminopyrine, phenazone and phenylbutazone.

§Coxibs: celecoxib, etoricoxib and valdecoxib.

¶Other NSAIDs: for example, aspirin, ibuprofen, naproxen, indomethacin, diclofenac, fenoprofen, meloxicam, mefenamic acid and nimesulide.

**For lansoprazole and rabeprazole, no intravenous solution is available: SPT with powder, IDT not possible.

††In case of history with severe reaction, test first 1%; NA, not applicable or no test concentration recommended.

causing severe reactions or where literature/experience is lacking, skin tests should use nonirritant concentrations of the drug. This can be established using different dilutions of increasing drug concentration. The nonirritant drug concentration should ideally be established in healthy controls [reviewed in (2)]. Where the drug is available only in tablet, capsule or topical form, only SPT and/or patch test can be performed (moderate/strong).

There are no standardized protocols or data on the optimal drug concentration available for skin testing using drug solution prepared from an oral formulation (moderate/weak). The common practice is to dissolve the tablet/capsule content in 0.9% saline and use the maximum concentration achievable to make the test as sensitive as possible (12). Most drugs are poorly soluble in water, and it is often the saturated suspension that is used. It is important to make an accurate record of the method used (e.g. suspension prepared by dissolving ground up 500 mg tablet in 10 ml 0.9% saline at room temperature for 'X' min/h/overnight). This will facilitate comparative/standardize studies (high/strong). A universally accepted recommendation regarding solvents and concentrations is currently impossible (low/strong).

The vehicle providing optimal skin penetration for drug patch test has not been formally evaluated. The most common method is to use finely ground tablet of liquid drug to make different test concentration of 5–30% in petrolatum. It is important to mix well to obtain a homogenous preparation (high/strong) (12). Drugs may be irritant to the skin, and it is necessary to establish in healthy controls (ideally ≥ 20) the nonirritant concentration (13).

A positive skin test to nonirritating drug concentrations is consistent with an allergic mechanism, although the precise test accuracy (sensitivity/specificity) remains unknown (high/strong). Test accuracy cannot be determined without the numbers of true positive and negative test results, which would require provocation tests in all patients including those with positive skin tests. The negative predictive value is dependent on the pretest probability and is not helpful without this information in selected patient groups. ST is not helpful in situations where the sensitivity is very low, because of the increased risk of false-negative reactions. In the absence of this information, we have aimed for nonirritating skin test concentrations, with the highest possible test specificity (if possible exceeding 95%). Because of limited sensitivity, a negative skin test does not rule out drug hypersensitivity (high/strong). Before re-administration, a drug provocation test following ENDA recommendations is necessary (high/strong) (5).

Antibiotics

Recommendations for the diagnosis of betalactam hypersensitivity have recently been updated, and nonirritant skin test concentrations are shown in Table 1 (moderate/strong) (6). However, several studies indicate that for cefuroxime, ceftriaxone, cefotaxime, cefazidime, cefozolin, cephalexin, cefaclor and cefatrizine, but not cefepime, concentrations up to 20 mg/ml are probably also not irritant and might improve the sensitivity without affecting the specificity (14, 15).

The diagnosis of penicillin hypersensitivity is only confirmed in a fraction of patients claiming such reactions, especially when parents report their children's history (high/weak) (16). Initially, specific IgE is determined for confirmation. However, skin testing remains the most important method for confirming betalactam allergy. Immediate hypersensitivity reactions to betalactam can be due to reactivity to the betalactam moiety or the side chain. Testing with the penicillin polylysine and minor determinant mixture (MDM) appears adequate to establish the diagnosis, when benzyl penicillin is the suspected antibiotic and the reactivity is against the betalactam moiety. However, the reactivity could be against the side chain (e.g. aminopenicillin side chain in

amoxicillin) in which case tests for penicillin polylysine and MDM are negative, but the suspected betalactam positive (17). Amoxicillin has replaced penicillin polylysine and MDM as the most important determinant of penicillin allergy (18, 19). For optimal sensitivity, we recommend SPT and IDT with penicillin polylysine, MDM, benzyl penicillin, amoxicillin and the suspected betalactam (high/strong) (6).

Betalactam may be used in combination with a betalactamase, for example, Amoclav/Augmentin (amoxicillin and clavulanic acid). A reported reaction to Augmentin could therefore be due to an allergy to clavulanic acid and not amoxicillin (20). Skin testing should be carried out against the original drug and individual component of the antibiotic combination.

As with penicillins, skin tests with nonirritant concentration of cephalosporins have a higher sensitivity compared with NIHR (high/weak). For the investigation of adverse reaction to cephalosporin, it is recommended that the suspected cephalosporin, PPl, MDM and betalactams with similar side chains are used (moderate/strong) (6).

In severe reactions (anaphylaxis, severe systemic symptoms) to antibiotics, it is strongly advised that SPT is initially performed after IgE testing. If negative, IDT should start antibiotic at dilutions of 1/1000 or 1/100. This is to reduce the risk provoking systemic symptoms (high/strong) (6).

In NIHR, skin testing with penicillin polylysine and MDM is scarcely useful (moderate/strong). IDT with delayed readings generally has a higher sensitivity than patch test with similar specificity (low/weak) (21). The value of patch test in addition to IDT remains controversial. Negative IDT but positive patch test has been observed by some members of the group, and in NIHR to betalactam, most of the group recommend additional patch test (low/weak).

The sensitivity of betalactam skin tests differs between studies (high) and may be as high as 70% in immediate and 10–30% in NIHR (low/weak) (22, 23). When the skin test is negative, a diagnosis cannot be established without a drug provocation test (strong).

For most nonbetalactam antibiotics, the value of skin tests appears to be uncertain (moderate/weak) and false-positive reactions may occur when the antibiotic is tested at high concentrations.

Skin prick tests and IDTs with undiluted intravenous solutions for the majority of nonbetalactam antibiotics may be irritant, and lower dilutions should be used (high/strong) (24, 25). In the literature, reports on the highest nonirritant dilutions vary greatly and sensitivity appears to be low (moderate/strong) (24, 26). Recommendations on concentrations are currently not possible, and concentrations used in the literature are given in Table S1 (26, 27). Nonimmediate hypersensitivity reactions to nonbetalactam antibiotics, studied using patch tests with different concentrations of crushed tablets in petrolatum, have been reported to be nonirritating (moderate/strong) (27).

Nonsteroidal anti-inflammatory drugs

The vast majority of immediate hypersensitivity reactions to NSAIDs (excluding pyrazolones) are not due to an IgE-mediated mechanism, but are thought to be related to an aberrant arachidonic acid metabolism (high/strong) (9). In these cases, SPT and IDT are usually negative (high/strong). Therefore, it is not recommended in routine clinical practice to skin test nonpyrazolone NSAID (moderate/strong). Instead, drug provocation test with the suspected NSAID is the recommended diagnostic test and this is in line with ENDA recommendation (5, 9). The irritating potential of all NSAIDs appears to be low in SPT, and the specificity is thus high (≫95%). For IDT, 0.1 mg/ml appears to be not irritating to the skin (moderate/weak; Table 3). Higher concentrations of NSAID appear irritant (low/weak).

Positive skin and/or laboratory tests may be seen in up to 40% of patients with immediate hypersensitivity reactions to pyrazolones (high/strong) (28). IgE-mediated anaphylactic reactions are exceptional with nonpyrazolone NSAID such as diclofenac or ibuprofen.

All NSAIDs can cause NIHR, and these can be detected by positive patch tests (high/strong) (29). The relative incidence of allergic and nonallergic reactions is not well studied (moderate/weak). Patch tests with up to 10% NSAID in petrolatum do not seem to be irritant to the skin (Table 3) (moderate/strong). Concentrations up to 30% may be tolerated (low/weak), although the additional value of using the higher concentration is questionable (moderate/weak). Undiluted celecoxib appears irritant, and this may be the case for other NSAIDs (moderate/weak) (30).

Opioids

Opioids induce nonspecific direct histamine release, leading to false-positive SPT and IDT (strong). To minimize erroneous reading due to histamine release or irritant reaction, it is proposed that increasing dilutions of the suspect opioid (end point titration) are used when investigating immediate hypersensitivity reactions (high/strong).

The value of skin tests with opioids remains unproven, and optimal skin test concentrations are unknown (moderate/strong) (31). For fentanyl and its derivatives, the undiluted solution is recommended (Table 2) (moderate/strong), and for morphine SPT, 1 mg/ml is proposed (low/weak). In an unpublished study of 16 normal controls, 0.1 μg/ml morphine, 0.01 μg/ml codeine, 0.5 μg/ml pethidine and 1.7 μg/ml tramadol were found to be nonirritant to the skin (AB personal communication; low/weak).

Positive patch tests to opioids in NIHR have been described. There is no universal agreement on the optimal vehicle (aqua, petrolatum, ethanol) or test concentration (high). 3% and 5% diacetylmorphine in petrolatum have been shown to be nonirritant (low/weak) (32). 5% morphine in petrolatum is nonirritant and elicited positive reactions (low/weak) (33). There appears to be skin test cross-reactivity between morphine and 5% codeine phosphate but not with 5% pentazocine and 5% tramadol (low/weak). No recommendation can be given for optimal conditions for codeine or buprenorphine (high).

Perioperative drugs

The perioperative drug skin test concentration recommended is listed in Table 2, which is derived from literature published in 2002–2009 and is probably the maximum nonirritant drug concentration. There have been numerous multicentre studies from France under the auspices of Societe Francaise d'anesthesia et de Reanimation (34), whose recommendations have been updated recently (7) and these have been endorsed by ENDA. However, their skin test criteria differ, and further studies, preferably multicentre studies, are needed to harmonize and standardize the test criteria (moderate/strong).

There are few studies in healthy volunteers but these differ in test methods and diagnostic criteria, making comparison of data difficult (high/strong). Geographical differences exist in the incidence of reactions to neuromuscular blocking agents, probably partly due to pholcodine exposure, which may increase risk of sensitization (35).

Neuromuscular blocking agents can induce nonspecific direct histamine release in the skin, increasing the possibility of false-positive tests, especially in IDT (high/strong). Preoperative screening or testing in patients without prior reactions may lead to false-positive tests/conclusions and should not be carried out routinely (high/strong).

Cross-reactivity has been reported between neuromuscular blocking agents in up to 60–70% of cases (moderate/strong) (36). It is recommended that in the investigation of the suspected drug, also other available neuromuscular blocking agents should be tested simultaneously to rule out cross-reactivity (high/strong) and to identify a safe alternative (moderate/weak). Chlorhexidine is an integral part of the perioperative test panel in some centres. Validated nonirritant chlorhexidine concentration is listed in Table 3 (high/strong) (37, 38).

The investigation of adverse reaction to perioperative drugs should be in specialist centres and in close collaboration with anaesthetists (moderate/strong). Investigations should include SPT $\pm$ IDT with all substances the patient was exposed to including antibiotics, colloids, latex, disinfectants (e.g. chlorhexidine), opioids, patent blue, etc. (high/strong).

Specific IgE to latex, chlorhexidine, penicillin determinants, pholcodine and muscle relaxants are well-validated widely available tests and should be an integral part of the investigations.

As perioperative reactions are almost exclusively immediate hypersensitivity reactions, there are no recommendations for the investigation of apparent NIHR to perioperative drugs.

Local anaesthetics

Confirmed immediate hypersensitivity reactions to local anaesthetic (LA) are rare. Undiluted LA appears nonirritant in SPT. Undiluted LA was reported to give negative IDTs in 90–95% of patients and in >90% of controls (39, 40). Intradermal test with 1/10 diluted LA has been shown to be nonirritant. It is recommended that neat LA is used for SPT and 1/10 dilution LA for IDT (Table 3) (high/strong). Skin prick test and IDT should not be performed with LA containing vasoconstrictors like adrenaline, as they mask a local wheal and flare reaction (high/strong). Excipients in LA, such as bisulphites, have been reported to exceptionally cause anaphylaxis and delayed-type reactions. To diagnose these reactions, bisulphite skin tests are of no diagnostic value and oral provocation test with metabisulphite is necessary to confirm/exclude the diagnosis (moderate/strong).

Cross-reactivity has been reported between ester-type LA but not between amide LA. In confirmed LA allergy, other LAs should be tested to identify an alternative (moderate/strong). A drug provocation test with the alternative LA is necessary (high/strong). In NIHRs to LAs, it is recommended that IDT is performed with 1/10 dilution LA and patch test with neat LA (high/strong).

Heparins, heparinoids and other anticoagulant drugs

Neat heparins appear nonirritant and can be used as such for SPT (high/strong). Intradermal test using 1/10 dilution appears irritant (41). If 1/10 dilution has been used, it is advised that further tests be carried out with 1/100 and 1/1000 dilution to exclude an irritant reaction (moderate/weak). Immediate-type IDT reactions may also be caused by chondroitin sulphate that may present due to incomplete purification of heparins (low/weak).

Nonimmediate hypersensitivity reactions to subcutaneous (sc) injection of heparins present as erythematous or eczematous plaques at the injection sites (high/strong). If heparin treatment is continued, there is a risk of a generalized eczema or exanthema (high/weak).

For skin testing, it is recommended that a panel of different heparin and heparinoid preparations, including an unfractionated heparin, low molecular weight heparins and heparinoids, are used (moderate/weak). Patch tests can be performed using undiluted heparin or heparinoids sc or iv solutions (high/strong). A 1/10 dilution is recommended for heparin and heparinoid IDT (Table 3) (moderate/strong). Lower concentrations decrease the sensitivity of IDT (high/strong) (41). Heparin skin testing is contraindicated in patients with heparin-induced thrombocytopenia (high/strong).

The literature is poor on skin testing with vitamin K antagonists, and it is not possible to make any specific recommendation. Because of low specificity, IDTs are not useful for screening patients with protamine-associated anaphylaxis (low/weak) (42).

Iodinated contrast media, gadolinium chelates and dyes

Skin testing is recommended in the work-up of iodinated contrast media hypersensitivity (high/strong). It is advisable to use a panel of ICM so as to identify cross-reactivity and safe alternatives (high/strong) (8).

Skin prick tests and patch tests should be performed using undiluted solutions (high/strong). For IDT, a 1/10 dilution of ICM is recommended, as undiluted contrast media may be

irritating (weak/high; Table 3). In delayed reactions, both delayed reading IDT and patch test should be carried out to enhance sensitivity (moderate/high). False-negative skin tests in NIHRs do occur (43).

It is not possible to recommend firm test concentration for gadolinium chelates. For SPT, a neat solution appears nonirritant (moderate/weak). For IDT, neat gadolinium has been reported to cause false-positive reactions in normal controls; thus, a 1/10 dilution has been used (44). There are no reports of NIHR to gadolinium chelates.

Experience with blue dyes is limited (45). Skin prick test has been performed using undiluted solutions (Table 3) and IDT using up to 1/10 dilution for patent blue dye and 1/100 for methylene blue dye (moderate/weak). Cross-sensitivity has been described, and we therefore recommend testing other dyes (low/strong).

Literature on skin test to fluorescein is poor. Fluorescein has been used neat for SPT and 1/10 for IDT in the diagnosis of allergy (low/weak) (46).

Anticonvulsants

IgE-mediated immediate hypersensitivity reactions to anticonvulsant drugs do probably not exist. For NIHR, patch test with a concentration of up to 10% of the pure substance appears to be nonirritating to the skin (moderate/strong) (Table 3). In severe anticonvulsant hypersensitivity reactions, patch test may result in a flare-up. In such cases, the initial test concentration should be diluted to 1% (moderate/strong). The sensitivity appears highest for carbamazepine and phenytoin and lower for phenobarbital and lamotrigine (moderate/weak). Clinical cases suggesting cross-reactivity between anticonvulsants have been reported (47), but it has been discussed that those may rather represent flare-up reactions (48). The sensitivity of patch test seems unaffected by the vehicle used (petrolatum, normal saline, water or ethanol; moderate/weak).

Abacavir

Patch testing with 10% abacavir revealed a specificity of 100% and sensitivity of 79% for patients with confirmed HLA-B*5701 genotype (49).

Chemotherapeutic drugs

Except for platinum salts, an IgE-mediated hypersensitivity to chemotherapeutic drugs has not been demonstrated (moderate/strong).

Skin tests are useful for platinum salt-related immediate hypersensitivity reactions (moderate/strong) (50), while for other chemotherapeutic drugs, experience is limited and test results often negative (low/weak).

The irritant potential of chemotherapeutic drugs appears to be low. For platinum salts, the use of undiluted drugs is recommended (high/strong). For other chemotherapeutic drugs, SPT with undiluted agents is probably nonirritant, but due to toxicity concerns, a general recommendation cannot be given.

For IDT, a 1/10 dilution of most chemotherapeutic drugs is nonirritant and may be used in clinical practice (moderate/strong), whereas higher concentrations appear to be irritant (MP, personal communication; low/weak). Patch tests are almost always negative in NIHRs and are not recommended in clinical practice (low/weak).

Biological agents

The literature on skin testing for biological agents is poor. However, there are satisfactory data on nonirritant test concentrations for the TNFα antagonists adalimumab, etanercept and infliximab and omalizumab.

The highest published nonirritant concentrations for adalimumab (SPT 50 mg/ml, IDT 5 mg/ml) (51), etanercept (SPT 25 mg/ml, IDT 5 mg/ml) (51), infliximab (10 mg/ml) (52) and omalizumab (12.5 μg/ml) (53) can be used for skin testing (moderate/weak). Patch test has been performed using undiluted adalimumab and is recommended for NIHRs (low/weak).

Hormones

Glucocorticoids rarely cause immediate hypersensitivity reactions, and a general recommendation for all glucocorticoids is currently not possible. Glucocorticoids may be formulated with other drugs, for example, LAs and contain excipients like macrogol. Skin test must include the additional drug(s) and excipient in the panel. Skin test with methylprednisolone (SPT 2 mg/ml and 20 mg/ml, IDT 0.2 mg/ml and 2 mg/ml) and triamcinolone (SPT 4 mg/ml and 40 mg/ml, IDT 0.4 mg/ml and 4 mg/ml) has been reported.

Hypersensitivity reactions to glucocorticosteroids tend to be NIHRs (high/strong). Glucocorticoids may suppress skin reactivity (54) and give paradoxical reading of greater reactivity at lower test concentration and at later time points (moderate/strong) (55). Thus, the patient should be instructed to come for a repeat visit, if test reactions do develop after 4–7 days. The significance of dose, vehicle, occlusion time and reading time is only partially evaluated (moderate/strong) (55). Two steroids (budesonide and tixocortol) have been well studied and used at 0.1 mg/ml in the standard patch test panel (high/strong). There is cross-reactivity between the different glucocorticoids, and in NIHR, 4 cross-reactive groups have been proposed (high/strong) (54). Glucocorticoids' cross-reactivity has also been described for immediate hypersensitivity reactions (56).

Up to 28% of asymptomatic insulin users may be IDT positive in IDT to 1/10 insulin (57). The clinical significance of positive insulin skin test should be confirmed by drug provocation test (moderate/weak). Insulin additives such as protamine have to be considered and tested. The literature is scanty on skin test for other therapeutic hormones. It is not possible to make any specific recommendation (low/weak), and skin testing remains experimental (low/weak).

Blood products including immunoglobulins

Blood products including immunoglobulins may induce immediate hypersensitivity reactions. They result from preexisting IgG antibodies to human proteins and complement activation and manifest as haemolytic anaemia/shock (blood group antibodies, anti-IgA), fever (cytotoxic antibodies). There are limited data on skin testing with sera and immunoglobulins, and definite recommendations on the value and test concentrations are not possible.

Vaccines

Adverse reactions to vaccines may be due hypersensitivity to the vaccine itself, excipients (e.g. gelatin), added antibacterial (neomycin) or proteins resulting from culture methods (ovalbumin from yolk sacs in influenza, herpes simplex and yellow fever, but not in measles, mumps, rubella or rabies vaccines) and may manifest as acute urticaria, angio-oedema and anaphylaxis (58). Although very rare, vaccine components, that is, immunizing agents, egg proteins, gelatin and other potential allergens may induce immediate hypersensitivity reactions, such as immediate urticaria, angio-oedema and anaphylaxis (58).

Skin prick test with neat vaccine and IDT with 1/100 dilution have been shown to be nonirritant, and it is recommended that these concentrations are used (low/weak) (59).

Skin prick test ± IDT with immediate reading should be performed in suspected reactions using the suspected vaccines, excipients such as gelatin, and neomycin when indicated. In individuals with a history of serious systemic reaction to egg and the vaccine needed by the patient is derived by yolk sac culture (e.g. influence, yellow fever, herpes simplex), the investigation would need to include a risk assessment of ovalbumin allergy (low/weak).

Vaccine excipients have been reported to induce eczematous or indurated NIHR (aluminium hydroxide, thimerosal, phenoxyethanol and formaldehyde). The pathogenesis of late-onset urticaria, angio-oedema and nonurticarial rashes is not known.

Additives

Several cases of anaphylaxis to additives such as polysorbate 80, carboxymethylcellulose and macrogols/polyethylene glycols have been described. Although uncommon, hypersensitivity should be considered, if a patient shows reaction to different unrelated drugs containing the same additive (high/strong). In such cases, skin testing with the active drugs as well as the additive is recommended (moderate/strong).

0.5–1.0 mg/ml polysorbate 80 in SPT and IDT and 5–10 mg/ml carboxymethylcellulose have been reported to be nonirritant (weak/low). In carboxymethylcellulose NIHR, 1 mg/ml carboxymethylcellulose was reported to elicit a positive delayed reading IDT and to be nonirritant in 6 normal controls (60).

Undiluted PEG 400 has been used in the investigation of immediate hypersensitivity reactions to macrogol/PEG and found to be nonirritant (61). However, IDT with methylcellulose and macrogol may be complicated by severe systemic reactions (62). Skin prick test up to undiluted macrogol/polyethylene glycol 4000 have been reported (61). At present, it is not possible to recommend optimal skin test concentration for these additives.

Proton pump inhibitors and H_2 antihistamines

Most reported reactions to proton pumps inhibitors and H_2 antagonists are immediate hypersensitivity reactions (63). However, the specificity of skin tests has to be determined (low/weak). Undiluted and 1/10 parenteral proton pump inhibitors appear nonirritant (moderate/weak) (63). There are inadequate data on H_2 antagonist skin test concentration (low/weak): 1/100 appears nonirritant but not 1/10 dilution, especially for nizatidine. Currently, it is not possible to make specific recommendations for these drugs (low/weak). Patch test with proton pump inhibitors at 10–50% of the drug in petrolatum is nonirritant (moderate/weak).

Antihypertensive drugs

Antihypertensives rarely cause immediate hypersensitivity reactions, and skin tests with calcium channel blockers and beta-blockers appear not to be useful in the investigation of hypersensitivity to these drugs (moderate/weak). Most confirmed hypersensitivity reactions to antihypertensive drugs (beta-blockers and calcium channel blockers) are NIHRs presenting with exanthemas (high/strong), and positive patch tests have been described in some case reports. Patch tests with calcium channels blockers and beta-blockers of 1–30% drug in petrolatum appear nonirritant (moderate/weak). Reports about hypersensitivity reactions to other anti-hypertensive drugs (such us diuretics, alpha-blockers, ACE inhibitors and angiotensin receptor blockers) are scarce or nonexistent and do not allow any recommendations to be made (high/strong).

Discussion

Skin tests have the potential to locally reproduce *in vivo* an IgE-mediated or T-cell-mediated drug allergy. Interpreted in the clinical context, skin tests using nonirritant drug concentrations can confirm or exclude the diagnosis of drug allergy. *In vitro* laboratory tests may not be available, restricted in repertoire, not well validated or of research nature. Drug provocation tests are time-consuming, associated with appreciable risk to the patient and not standardized for NIHR. In our review, we note the paucity of literature on skin drug test concentration and method protocols. However, we have by consensus been able to agree and recommend test concentration for many drugs that are listed in Tables 1–3 (moderate/strong). In addition, structured and detailed information on all relevant studies from the literature is available on the website http://eaaci.net/sections-a-igs/ig-on-drug-allergy/resources.html on the homepage of the Drug Allergy Interest Group of the EAACI (Table S1).

Table 4 Drugs for which the value of skin tests has not adequately been demonstrated

Antihypertensive drugs
Biologicals other than anti-TNF preparations and omalizumab
Hormones, corticosteroids and insulins
Nonbetalactam antibiotics
Nonplatinum chemotherapeutics
NSAIDs other than pyrazolones for immediate reactions
Opioids
Sera, immunoglobulins and vaccines

NSAID, nonsteroidal anti-inflammatory drug.

For many drugs, where the literature is confined to small case series, case reports, personal experience or nonexistent, no specific recommendation is made or should be regarded as tentative until further review. For some drugs, the value of skin tests has not been sufficiently demonstrated (Table 4). The optimal vehicles for skin test reagents and data on stability remain unknown. Drug reactions may be due to its metabolites, and testing using drug metabolites should be an area for further research.

For most drugs, particularly for betalactam antibiotics, the sensitivity of skin testing (SPT, IDT, patch test) is significantly higher for immediate hypersensitivity reactions presenting as anaphylaxis or urticaria compared to NIHRs such as exanthemas (high/strong).

Skin prick test is relatively simple to perform and shows acceptable specificity for most of the reviewed drugs with the exception of drugs with irritant or histamine-releasing properties such as quinolones and opioids (high/strong). It is usual and advisable to exclude specific IgE first, if available, then do SPT especially in individuals presenting with severe systemic reactions, and only if negative, proceed to IDT. Fatal systemic anaphylaxis has been reported after IDT without preceding SPT (64). Intradermal test has a high sensitivity, but also a higher risk of inducing irritant reactions and false-positive results. For NIHRs, the patch test has an equal or slightly lower sensitivity than IDT with delayed readings. Patch test is especially helpful as an additional test method when no intravenous drug solutions are available for an IDT.

When nonirritant concentrations are used, skin tests in drug hypersensitivity are generally characterized by a relatively low sensitivity and a high specificity (high/strong). In this review, we aimed to select skin test concentrations with the highest possible specificity (>95%) and thus a high positive predictive value. Unfortunately, the sensitivity of skin tests to most drugs is low. Therefore, in cases of negative skin tests, drug allergy cannot be excluded and a drug provocation test has to be considered. In drug skin test, it is best that the skin test concentration achieves higher specificity, which may be at the expense of sensitivity (high).

In addition to standardizing skin test concentration, there is a need to be able to reproduce test results not only in a single but amongst different centres. A study of the test protocol in different centres in Europe showed that there are substantial differences in performance and interpretation of skin tests (65). The ENDA group has developed a generic skin test protocol for performing, reading and interpreting the results (2), and this has been adopted by several centres. Tables 1–4 and recommendations in this paper are based on this method. Other published techniques and protocols are available in the online Table S1, for example, the multicentre French study on perioperative drugs (34). Studies are in progress in Europe to validate and further standardize the ENDA/EAACI skin test protocol in particular IDT. Such studies will enable results to be scientifically compared and exchanged. Skin testing in healthy volunteers is essential to establish nonirritant test concentration and determine test sensitivity and specificity.

In conclusion, it has only been possible to obtain a high to moderate level quality of evidence and strong (strength of) recommendation for specific skin test concentrations for a few drugs. For most other drugs, there is a definite need for multicentre studies on skin test concentrations in patients and in unexposed controls. The recommendations will need regular review and standardization. In specialized centres, we recommend testing all patients with a suggestive history of drug allergy with the concentrations listed in Tables 1–3 as well as in Table S1 on the website to gain further experience.

Conflict of interest

There has been no conflict of interest for any author.

Author contributions

See Appendix 1.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Relevant literature data on reported skin test concentrations to systemically applied drugs with information on the test preparation, number of patients and controls, test details and type of study.

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Appendix 1. Author responsibility

Analgesics, NSAID: Brockow K
Antacids, cardiovascular, Bonadonna P, Lombardo C
Anticoagulants, protamine: Trautmann A
Anticonvulsants, Schnyder B
Biologicals: Campi P, Testi S
Betalactam antibiotics: Torres M, Blanca M
Chemotherapeutics: Pagani M
Contrast media, dyes, gadolinium, fluorescein: Demoly P, Chiriac AM
Hormones: Aberer W
Local anaesthetics: Ring J, Grosber M
Nonbetalactam antibiotics: Cernadas JR, Castro E
Opioids:Scherer K, Bircher A
Perioperative drugs, muscle relaxants: Garvey LH, Mosbech H, Nasser S, Mertes M
Antiseptics, additives: Grosber M, Garvey LH
Sera, vaccines, immunoglobulins: Bilo B
Overall control of integrity: Barbaud A, Terreehorst I, Atanaskovic-Markovic M, Romano A, Garvey LH, Gooi J
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