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SKIN TESTS IN THE WORK-UP OF CUTANEOUS ADVERSE DRUG REACTIONS: A REVIEW AND UPDATE

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SUMMARY

Skin tests, including patch tests (PTs), prick tests and intradermal tests (IDTs), are useful to identify the culprit(s) of a cutaneous adverse drug reaction (CADR), and to determine (a) safer alternative drug(s). PTs have a low sensitivity but are valuable to investigate maculopapular exanthema (MPE), as well as severe CADR, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and (especially) acute generalized exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS). To ensure their specificity at least 10 controls should be performed. Prick tests are mainly used in the evaluation of immediate-type hypersensitivity, and can be performed with all drugs, except opiates. IDTs can be used to explore immediate and delayed-type hypersensitivity, if an injectable form of the drug exists. Except for SJS/TEN, IDTs should be performed by injecting 0.02 mL of the drug. We here provide a practical up-to-date review on the use of these skin tests in the work-up of CADRs. Numerous negative controls for drug PTs, prick tests and IDTs, as well as criteria for the immediate and delayed positivity of the latter, are included. It should be emphasized that a negative result never excludes the potential responsibility of a drug in a CADR.

Key words: cutaneous adverse drug reactions (CADRs), diagnosis, drug skin tests, patch tests, prick tests, intradermal tests, delayed-type drug hypersensitivity, immediate-type drug hypersensitivity, review.

1. INTRODUCTION

Drug skin tests are useful in the work-up of cutaneous adverse drug reactions (CADR). They can be used to identify the responsible drug(s), to study cross-reactivity between drugs, and to determine (a) safer alternative drug(s). Moreover, drugs testing negatively can be used to guide drug challenges (provocation tests), which still constitute the gold standard in the work-up of drug hypersensitivity, always performed under surveillance in a hospital setting, and only for non-severe CADR.

In the literature, unfortunately, quite large variations exist in the way these particular tests are performed, making comparison between centers difficult. Moreover, there are also clear differences in the approach to CADR between Europe and North America (1).

In this review we have summarized and updated the current knowledge on the value of skin tests in the work-up of CADR, according to international guidelines (recommendations) supplemented with recent publications (2,3). More specifically, we detail, in a practical way, how to ensure good sensitivity (i.e., to avoid false-negative results) and specificity (i.e., to avoid false-positive results) when performing these tests, the latter by including numerous negative controls according to recent papers and personal experience. Besides being relevant for the clinic, these data may also enable comparison of results whenever these are reported in the literature.

For drugs for which only limited data on specificity are available in the literature, or if these are not represented in any of the aforementioned international recommendations, we additionally performed a PubMed query using the following key words: #a given drug (class) AND drug skin test, #a given drug (class) AND patch tests; #a given drug (class) AND prick tests; # a given drug (class) AND intradermal tests; # a given drug (class) AND skin tests. Only publications detailing 10 or more controls were considered relevant.

2. WHEN SHOULD DRUG SKIN TESTS BE PERFORMED FOLLOWING THE RESOLUTION OF A CUTANEOUS ADVERSE DRUG REACTION (CADR)?

Although drug skin tests can occasionally still be of value (i.e., result in positive reactions) several years after the occurrence of a CADR, including urticaria and angioedema, it is generally recommended to perform them at the earliest 4 weeks following the disappearance of the CADR, and preferably within one year after the event (2,3).

When the CADR concerned a drug reaction with eosinophilia and systemic symptoms (DRESS), the tests should be performed at least 6 months after the disappearance of this particular CADR, and in the absence of high virus replication (4,5).

In immediate-type drug hypersensitivity (IHS) to beta-lactam antibiotics, skin reactivity decreases rapidly after the onset of the (iatrogenic) event, and 50% of patients appear to have lost their skin reactivity when they are re-tested one year after the first evaluation (6). Romano *et al.* (7) showed that, of 72 subjects with positive skin tests after an IHS to cephalosporins, even 62.5% lost their skin reactivity when they were re-tested within 1-5 years.

In delayed-type drug HS the loss of cutaneous reactivity has not been so well studied, but some data indicate that this appears to be longer lasting. Two patients who had experienced a DRESS were re-tested, 9 months and 11 years, respectively, following their first investigations, and their patch tests had remained positive (4). Twenty patients (9 males and 11 females, with a mean age of 54.6 years old), who had suffered from a maculopapular eruption (MPE, n=18), DRESS (n=1), and acute generalized exanthematous pustulosis (AGEP, n=1) due to delayed-type HS from antibiotics, were re-tested, 2 to 15 years after their first investigations (mean delay of 6 years) and in 17/20 patients PTs still showed positive reactions (8).

3. WHEN CAN DRUG SKIN TESTS BE AVOIDED BEFORE DRUG CHALLENGES (PROVOCATION TESTS)?

In children presenting with only a “mild” MPE (exanthema), some authors have argued that drug challenges or provocation tests could be done without performing any drug skin tests beforehand (9). However, a “mild” MPE indicates that the clinical reaction was not associated with any (central) facial edema, did not involve more than 60% of the body’s surface, and was not associated with any lymphadenopathy, high fever, nor arthralgia. Moreover, no laboratory abnormalities, such as eosinophilia, atypical lymphocytes, or liver and kidney alterations should have been present during the CADR.

In 48 adults who had experienced a “low risk” CADR, and had been labelled as “penicillin allergic”, provocation tests without any skin tests beforehand were performed and appeared to be well-tolerated in 47/48 cases; the one remaining patient had only experienced a mild, periocular erythema and edema (10). However, at this time, such approach cannot be universally recommended as it concerned only a limited number of patients, and the “low-risk” CADR involved “non-specific” (undefined) rashes, pruritus or urticaria, or an unknown reaction dating back more than 20 years. This is quite different from what has been proposed in the beta-lactam allergy guidelines (11), i.e., “low risk ” CADR patients include children with mild MPEs (exanthema, see above), and adults with a palmar exfoliative exanthema.

4. WHICH FACTORS CAN INTERFERE WITH DRUG SKIN TEST RESULTS?

Some (topical) drugs and also ultraviolet (UV) exposure can decrease the skin reactivity of drug skin tests, PTs in particular. Possible interferences are detailed in **Table 1**. In IHS, the use of beta-blockers is a relative contra-indication when performing drug skin tests (i.e. prick tests, IDTs), although Fung et al. demonstrated the relative safety of performing prick tests in patients receiving beta-blocker treatment (12).

5. WHICH TESTS ARE USEFUL FOR WHICH PATIENTS?

Drug skin tests are only useful in CADR that display an immuno-allergic mechanism. They are of no value in the investigation of pruritus, vasculitis, drug-induced auto-immune diseases, drug-induced pigmentation, to investigate cross-intolerance to nonsteroidal anti-inflammatory drugs, and drug-induced bradykinin-mediated angioedema. Furthermore, the value of a given drug skin test depends on the clinical features of the CADR and also on the drug involved.

In IHS, it is usually recommended to sequentially perform prick tests, and subsequently, if these are negative, to continue with intradermal tests (IDTs) with immediate readings. Patch tests (PTs) are not recommended, and in the context of anaphylaxis PTs are even contraindicated, as they do not only demonstrate a poor value in IHS, but can even be dangerous, i.e., capable of re-inducing the adverse event. Indeed, anaphylaxis induced by PTs has been reported, for example with antibiotics (beta-lactams, neomycin, gentamicin, and bacitracin), and non-steroidal anti-inflammatory drugs (NSAIDs) (diclofenac) (2).

For delayed HS, there have been discrepancies between European and American methods (1). In delayed-type HS, in Europe, it is recommended to initially perform PTs, and subsequently, if these are negative, and it concerned a non-severe CADR, to continue with prick tests and IDTs with delayed readings. An international consensus has recently been reached (13), and its adapted conclusions are summarized in **Table 2**.

In severe CADR, PTs are absolutely useful in the work-up of DRESS and AGEP, whereas in toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), notwithstanding they can also be performed, their value appears to be lower. Importantly, as stated above, in DRESS, an allergy work-up should be done >6 months following the disappearance of this particular CADR (4). The use of IDTs in the investigations of severe cutaneous adverse reactions (SCARs) remains controversial, although a recent study confirmed, in a large population, the good tolerance of IDTs in the work-up of DRESS (14), that is, if they are performed to study the absence of drug cross-reactivity, and/or to eliminate multiple hypersensitivity to different drug classes (15).

6. DRUG PATCH TESTS

Drug patch tests (PTs) are performed, similar to the investigation of allergic contact dermatitis (ACD), with patch test preparations containing haptens, i.e., the drugs under investigation.

Prior to patch-testing, it has been recommended to stop the use of systemic corticosteroids, immunosuppressive drugs and ultraviolet (UV) exposure 1 month before, whereas topical corticosteroids can be continued up to one week before the application of the PTs (2,3) (**Table 1**).

For some drugs ready-to-use patch test preparations exist, usually dilutions at 10% in petrolatum (pet.), yet these are only available for a limited number of molecules (e.g. marketed by Chemotechnique, Vellinge, Sweden, and SmartPractice, Calgary, Canada). For most drugs, it is necessary to dilute them (i.e., preferably the marketed form as retrieved from the patients) “in-house”. However, as the stability of such PT materials has not been validated, it is recommended to prepare them not too long in advance, i.e., just before scheduling the patch test procedure. When the active ingredient of a commercialized drug is available in its pure form, and is diluted in petrolatum, it should be stable for one month if kept in the refrigerator.

There are numerous recommendations on the dilutions (concentrations) of the drugs that should be used (2,3). Two European guidelines have detailed how to patch test commercially available drugs, at 30% (2) or 20% (3) pet.

The concentration of 30% was chosen because it was the highest concentration that allows a real dilution in petrolatum (2). Although ideally a concentration of 10% of the active ingredient should be obtained, Brajon *et al.* (12) showed that the exact amount of active ingredient in “in-house” prepared PT preparations of commercialized drugs at 30% pet. actually varies quite a lot, i.e., from 0.05% to 30%, with 25% of such preparations having an active ingredient concentration of only <2%. Overall, we recommend a concentration of 30% (2) of the commercialized form of a drug, rather than 20% (3), also because it is the only concentration for which there exists a significant number of controls in the literature, often also providing the exact amounts of the active ingredient present in these particular “in-house” prepared PT materials.

From a practical point of view, and certainly if it is impossible to obtain a 10% active ingredient concentration of a given drug, we suggest, whenever using drug PTs with the 30% pet. dilutions of a commercialized drug, to always include the exact concentration of the active ingredient, also to enable a standardization of methods among different centers and thus a reliable comparison of results (16). Indeed, in multicenter studies using drug PTs it would be convenient to consider only the active ingredient concentrations. Of course, when the active ingredient exists in a pure form (e.g. in lyophilisate) it is recommended to use this and dilute it at 10% pet. (2).

Regarding the pure forms of some drugs, pseudoephedrine and carbamazepine, in particular, it is advisable to start with a 1% dilution, instead of the usual 10%, and this in order to avoid a relapse of the CADR; only if this concentration remains negative, higher concentrations -up to 10%- can be used (2,5).

Some other commercialized forms of drugs should also be diluted at lower concentrations than the usual 30%, but then mainly to avoid false-positive results. For example, the content of celecoxib capsules should be tested at 5% or 10% pet., and not higher (17). Captopril pills diluted at 1% pet., and chloroquine pills diluted at 30% pet. may occasionally induce false-positive results, again illustrating the need of using lower dilutions. Colchimax[®] (colchicine associated with tiemonium methylsulfate and opium) at 10% pet. also readily induces false-positive results, although its threshold of specificity remains unknown (18). Commercialized misoprostol should be strongly diluted, i.e., at 1% pet. (18). According to Shiny *et al.* (19), some anticonvulsants (e.g. sodium valproate), even when diluted at 1% in pet., might still induce irritant (false-positive) reactions.

For corticosteroids and steroid hormones, if PTs are negative when these were prepared in pet., it is advisable to dilute them in ethyl alcohol (2).

In ACD, when using PTs, some recommend the use of 20 μ g of haptens diluted in pet. (40 mg/cm²) and 15 μ L for liquid preparations (20). To date, however, for drug PTs, there is no recommendation to apply a particular amount or volume of drug PT preparations onto PT chambers.

In some centers physicians prepare the in-house drug PT, whereas others collaborate with their hospital pharmacy service. In this regard, it is interesting to note that Assier *et al.* reported that materials prepared by physicians led to equivalent results compared to those obtained with ready-to-use products commercialized by Chemotechnique (21).

Table 4 provides detailed information on the specificity of numerous drug PTs: we summarized the reported concentrations of active ingredients (AIs) of these drug PTs, and the number of negative controls obtained with these, illustrating their usefulness in clinical practice. Most of these data have been adapted from Brajon *et al.*'s publication (16), supplemented with additional negative controls from more recent papers (19, 22,23), and from the author's personal experience.

Similar to the PT procedure in ACD, drug PTs are mounted on PT chambers and (usually) applied on the upper back. Following an occlusion of 2 days (D) they are removed and read on D2 (30 minutes following removal of the tests), and on D4 or D5, with a D7 reading for corticosteroids. In fixed drug eruption (FDE), drug PTs are always applied in duplicate, that is, on the back but also on the residual lesional skin site ("in situ drug PTs") and read on D1 or D2 (24,25). The readings are performed according to the same ESCD criteria used in ACD, i.e., an irritant, negative, doubtful, or positive reaction (+ to +++) is scored for each drug PT (20). It is recommended to also perform a control patch test with the exact same vehicle used to dilute the drug PT material, as sensitization to for example petrolatum or ethyl alcohol, although exceptional, does exist (26).

In the case of a positive drug PT with a (usually 30% pet.) dilution of a commercialized drug, the manufacturer should be contacted to supply all the individual components, so that these can be patch-tested separately, in order to identify if the active ingredient and/or an excipient was responsible for the positive PT reaction. Patch-testing the excipients can be done according to the literature (27,28).

When investigating drug-induced photodermatitis, both drug PTs and drug photo-PTs with the suspected drug must be performed. It is recommended to perform the tests with a 1% (instead of 10%) concentration of the active ingredient, and for phenothiazines even lower concentrations (i.e., 0.1%) should be used (29). For drug photo-PTs UV-irradiation (5 J/cm² UVA) is performed upon their removal 2 days after their application (30). The reading

(according to the same criteria as mentioned above) is done 2 days after the irradiation. A non-irradiated control drug PT is usually also applied and removed after 2 days, and read as usual. It should be noted that drug photo-scratch PTs are more irritating to the skin, and appear to be non-superior to regular photo-PTs (30).

Drug PTs overall have a rather low sensitivity, but are generally well tolerated. They are valuable in the investigation of delayed-type HS caused by drugs, including maculopapular eruptions (MPE; exanthema), drug-induced eczematous eruption, systemic contact dermatitis (syn. systemic allergic dermatitis, SAD), baboon syndrome, symmetric drug-related intertriginous and flexural exanthema (SDRIFE; syn. flexural exanthema), eczematous reactions at drug injection sites, as well as in severe CADR, specifically AGEP and DRESS, but also -to a lesser extent- in TEN/SJS (**Table 2**) (5,13). As stated above, they are of no use in the work-up of pruritus or vasculitis induced by drugs, and should not be employed in the work-up of IHS such as angioedema and urticaria.

Although many drugs may give positive results when explored by PTs (5,16), some drugs remain almost always negative; notorious examples include allopurinol, salazopyrine and paracetamol (4,31).

A clinically useful summary and recommendation on the preparation, application and interpretation (according to ESCD guidelines, [2]) of drug PTs is given in **Table 3**.

7. DRUG PRICK TESTS

Performing a drug prick test means that the drug is introduced in the upper dermis, where it binds to specific immunoglobulin E (IgE), as such induces mast cell degranulation, resulting in a localized “wheal and flare” reaction.

Drug prick tests can be performed with any available form of a commercialized drug: pills (which should be reduced to a very fine powder), powdery capsule contents, liquids or parenteral (injectable) solutions. They can often be used undiluted, however, in high-risk patients (e.g. patients with immediate reactions to beta-lactam antibiotics) the drug preparations for prick tests should be diluted (11,32), and the tests should be initiated with concentrations at least at 1:10 of the usual concentration to avoid any (severe) systemic reactions (11). Moreover, for some particular drugs maximum concentrations of prick tests have been defined (see below).

Drug prick tests are always performed after cessation of antihistamines and topical corticosteroids at the skin test sites (33). Other drugs that may alter skin reactivity are summarized in **Table 1**. Concerning psychotropic drugs, imipramine and phenothiazines, but not escitalopram, fluoxetine, or sertraline (34), may decrease skin reactivity (33).

Drug prick tests are carried out on the volar surface of the forearm by putting the drug, i.e., a drop or a small amount of powder, onto the skin and then perforating it with a special lancet (2,3,33). The results are compared to those obtained with a negative control (0.9% serum saline) and a positive control (histamine). If there is a relative or global shortage of a given drug (e.g., expensive biologicals, COVID-19 vaccines), a prick-to-prick test with a remaining drop of the left-over drugs in used vials is a feasible alternative; the lancet is then dipped in the drug solution and immediately used to puncture the skin.

Although drug prick tests can be performed for virtually all drugs, a notorious exception are opiates. Moreover, non-specific mast cell degranulations have also been observed, at the usual concentrations, with certain antibiotics and anesthetic drugs. Moreover, some drugs, when prick-tested undiluted (as is) may result in irritant (false-positive) reactions; the maximum

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concentrations for several drug prick tests are highlighted in Table 5 (in the supplementary material). Regarding some excipients, prick tests with polyethylene glycols (PEG) can be diluted as follows: PEG 3000 (50% water/volume), PEG 6000 (50% water/volume), and polysorbate 80 (20% water/volume) (35).

The reading of prick tests is performed at 20 mins: it is considered positive if the papule (wheal) is $\geq$ negative control plus 3 mm, and if there is a surrounding erythema.

Prick tests are mainly of value for investigating IHS. Out of 236 investigations for drug allergies in children, prick tests had a low sensitivity of 6.9% and an average positive predictive value of 50%, but had a very good specificity of 98.8% and a negative predictive value of 85.7% (36).

Regarding the use of drug prick tests in the work-up of delayed-type HS, it should be mentioned that, occasionally, a prick test may be of value, and result in a delayed positive reaction, i.e., erythema and infiltration at the skin test location (4,5) after 24 or 48 hours. However, this has only rarely been reported in some cases of MPE, DRESS and AGEP (4,5).

8. INTRADERMAL DRUG TESTS (IDTs)

When performing drug IDTs a small amount of a drug is injected into the dermis. It can induce an immediate wheal and flare reaction, in case an immediate drug HS occurred, but it can also result in a late reaction (dermal infiltration at the injection site) in case the CADR concerned a delayed-type drug HS.

In most cases, drugs for IDTs are diluted in phenolated or non-phenolated serum saline, and a negative control with the solvent used for dilution must be performed. The actual dilution used to start the drug intradermal testing will depend on the severity of the initial CADR. In immediate reactions, drug IDTs should be performed only after ensuring that there is no reaction at the prick test site, and IDTs are then started with low concentrations. For example, in case of beta-lactams, in the context of immediate drug HS, it is necessary to start with a concentration at 1:1000 of the use concentration, or even lower (11).

After a survey (37), with the aim to refine the previously published European recommendations (2,3), details on the procedure of performing drug IDTs, including the used dose, have been published (38). Detailed in (**Table 6** in the supplementary material), these guidelines include the 5 following recommendations:

- (i) drug IDTs should be performed in a hospital setting (under supervision), and can only be done with drugs that are commercially available in an injectable form;
- (ii) in severe CADR, thought to have been provoked by a delayed-type drug HS, such as AGEP, DRESS and TEN/SJS, IDTs should not be performed with the drugs that are highly suspected;
- (iii) the recommended volume for injection is 0.02 mL;
- (iv) the diameter of the injection papule (wheal) should be measured immediately after injection (initial wheal = W_i). The developing reaction is then measured at 20 mins; at that time the IDT is considered positive if the diameter of the measured wheal (W₂₀) is greater than or equal to

the diameter of the $W_i + 3$ mm, and if there is a surrounding erythema, that should also be measured;

(v) in the case of delayed-type drug HS, IDTs can become positive on delayed readings, that is, if erythema and infiltration occur at the injection site at the 24 or 48-hour readings.

IDTs can result in irritant (false-positive) reactions. A position paper providing guidelines on drug concentrations for skin testing was published in 2013 (39). This paper did not differentiate between the non-irritating concentrations used in skin prick tests and IDTs for immediate versus delayed reactions (39). These thresholds were determined according to literature studies in which IDTs were performed using numerous different techniques. The most widely studied drug classes were beta-lactams, iodinated radiocontrast media (RCM), general anesthetics and heparins (**Table 7** in the supplementary material).

Amoxicillin, amoxicillin-clavulanic acid and ampicillin can be tested at concentrations up to 20 mg/mL, and cephalosporins, excluding cefepim, can be tested at concentrations up to 20 mg/mL (11,32,39,40). IDTs with macrolides (41-44), rifampicin (42) and quinolones (42,45) can also be very irritating to the skin. IDTs with diluted solutions are equally of interest with regard to glycopeptides (46), and they could be of value in IHS to proton pump inhibitors (PPIs) (47).

Concerning IHS to iodinated RCM: these agents can be tested with undiluted solutions in prick tests, yet at a dilution of 1:10 in IDTs (48-51). Concerning delayed-type HS to RCM, patch tests, (undiluted), can be useful, and IDTs (with delayed readings) can be performed with an undiluted solution (50). Gadolinium derivatives can be tested in a 1:10 dilution of the standard concentration (51).

In immediate HS, with heparin and heparinoids, IDT are done with a maximum 1:10 dilution, but in delayed HS, they can be done with 1:10 or undiluted heparins (52). Nevertheless, IDTs with these drugs are formally contra-indicated in case necrosis occurred at the sites of heparin injections. As a positive reaction is often delayed, readings must be performed after 72 hours, or later.

Corticosteroids can be intradermally tested at a 1:10 concentration (53-56). Higher concentrations, especially regarding corticosteroids with long-lasting effects, might induce skin

atrophy (53). Allergies to excipients, mainly carboxymethylcellulose and polysorbate, must also be considered and tested separately (27).

IDTs with insulins are tested at a concentration of 1:10 (57,58).

IDTs with platinum salts are specific for immediate readings with dilutions from 0.1 to 1 mg/mL, depending on the salt (59-60); however, non-specific erythematous infiltration can occur after 24 hours with these IDT dilutions. These delayed reactions appear to be non-specific, as was published regarding carboplatin at 1 mg/ml (61), and as has been observed with oxaliplatin (A. Barbaud, unpublished data).

IDTs with biologicals and cytokines are of little use (62). Thresholds for specificity with anti-tumour necrosis factors (TNF) have been reported at the following concentrations: infliximab ≤ 2 mg/mL, adalimumab ≤ 50 mg/mL and etanercept ≤ 5 mg/mL (62-64). Some papers have reported IDTs with rituximab (62,65) and tocilizumab (62,66,67). IDTs with interferons are generally thought to be non-specific; nevertheless, they do appear to be of interest (i.e., displaying good positive and negative predictive values [68]) in generalized exanthemas attributed to these molecules.

The thresholds for the specificity of IDTs with numerous drugs are reported in **Table 7** (in the supplementary material).

For general anesthetics, it is necessary that the same IDT methods are adopted. The BASCI group recommends injections of 0.03 mL resulting in injection papules with diameters between 4 and 6 mm (69). On the other hand, the injection of a volume of 0.03 mL to 0.05 mL, as recommended in another publication, that results in a 4 mm Wi diameter should be controlled (70). The recommendation advising the injection of a volume of 0.02 to 0.05 mL resulting in a Wi with a diameter of 4 mm is probably better, but also deserves control of the average diameter obtained and proposes a more limited volume variation (71). The recent EAACI guidelines for IDTs recommend performing an IDT with a fixed volume of 0.02 mL and consider results to be positive if there is an increase in diameter of ≥ 3 mm, compared to the original bleb after 20 minutes (72). In using this method, which is the recent European network for Drug Allergy (ENDA) method for IDTs, the thresholds of specificity are detailed in **Table 7** (in the supplementary material).

Carboxymethylcellulose can be tested by prick tests and IDTs at a concentration of 10 µg/mL (27,73).

Some drugs frequently induce irritant (false-positive) results upon intradermal testing. A well-known example are vaccines, a group of drugs for which skin tests have not been standardized, and their specificities are debated. Concerning immediate-type HS from vaccines: prick tests, or a prick-to-prick test, using the undiluted vaccine and when available, its excipients (gelatine, egg, PEG), can be performed. However, IDTs frequently induce irritant (false-positive) delayed reactions, with undiluted vaccines, also with some vaccines diluted at 1:10, and occasionally even at 1:100 (e.g. influenzae vaccine)(74).

False-positive IDT results have also been reported with the drug glatiramer acetate, within the context of IHS, at 200 µg/mL but also, in some cases, at 20 µg/mL. The threshold for specificity has not yet been determined for this molecule (75).

9. NEGATIVE PREDICTIVE VALUE (NPV) OF DRUG SKIN TESTS

As skin tests and provocation tests are not standardized, it is currently difficult to compare the results throughout the literature. For beta-lactams, the NPV is approximately 90% depending on the type of hypersensitivity and the methods used for drug provocation tests (11). For RCMs, the NPV varies from 80% to 97.3% (50).

10. CONCLUSIONS

We have provided an extensive and up-to-date practical review of drug skin tests in the work-up of CADR. Notwithstanding their usefulness, it is time to consider standardizing drug skin tests methods, to reliably determine the thresholds for specificity, to evaluate tolerance, and to compare the results from one center to another. For PTs, reporting results to concentrations of active ingredients (AIs) is essential. For IDTs, the only way to standardize the methods is to work on a known allergen dose, and not on injection-wheal diameters. Finally, it should be emphasized that a negative skin test never excludes the responsibility of a drug in the occurrence of a CADR.

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Table 1: Drugs that may interfere with skin test results and measures to prevent their effect.

	Patch tests (PTs)	Prick tests	Intradermal tests (IDTs)	When to stop before testing	Reference
Antihistamines	N	R	R	4 days (7 days for loratadine or desloratadine)	2,3
Topical corticosteroids on the skin test site(s)	R	R	R	7 days	2,3
Systemic corticosteroids	R	N	U	1 month	2,3
Immunosuppressive drugs	R	R	R	1 month	2,3
Phenothiazines	N	R	U	Up to 10 days	33
Imipramine	N	R	U	Up to 21 days	33
Dopamine	N	R	U	undetermined	33
Clonidine	N	R	U	undetermined	33
Ultraviolet (UV) exposure	R	R	U	Up to 4 weeks	33

R: reduced or no reactivity of the particular drug skin test.

N: no effect on reactivity of the particular drug skin test.

U: undetermined effect on reactivity of the particular drug skin test.

Table 2: Use of drug patch, prick, and intradermal tests for immediate and delayed-type hypersensitivity reactions (adapted from Barbaud [5] and Phillips et al. [13]).

	Patch tests (PTs)	Prick tests	Intradermal tests (IDTs)
Urticaria, angioedema, anaphylaxis	Not useful	Useful (IR)	Useful (IR)
Maculopapular eruption (MPE)	Useful (positive in 10-40%)	Limited value (DR)	Useful (DR)
Systemic allergic dermatitis	Useful	Not useful	Unknown value)
Baboon syndrome and SDRIFE	Useful (positive in 52-82%)	Limited value (DR)	Useful (DR)
Fixed drug eruption (FDE)	Useful with in situ application in the area of a previous reaction (positive in 40%) (24) ; when negative a repeated open application test (ROAT) can be performed (24)	Not useful	Not useful
Generalized bullous fixed drug eruption	May be useful	Contraindicated	Contraindicated
Acute generalized exanthematous pustulosis (AGEP)	Useful, sensitivity up to 58% (4)	Limited value (DR)	Potentially useful (DR)
DRESS	Useful (positive in 32-64%) dependent on the drug (4,31); advised 6 months after the disappearance of DRESS	Limited value (DR)	Contraindicated with the most highly suspected drugs DR; safety is currently unknown, yet could be interesting to investigate alternative (safer) drugs, or drugs that are lowly suspected (14)
SJS/TEN	Low sensitivity (<30%)	Unknown value (DR)	Contraindicated with the suspected drugs
Photosensitivity	Photo-patch tests (5 J/cm ² UVA)	No value	No value
Vasculitis	No value	No value	No value
Cross-intolerance to nonsteroidal anti-inflammatory drugs	No value	No value	No value
Flush due to corticosteroids	No value	No value	No value
Drug-induced and bradykinin-mediated angioedema (without wheals).	No value	No value	No value

DRESS: drug reaction with eosinophilia and systemic symptoms; SJS/TEN: Stevens-Johnson Syndrome/Toxic epidermis necrolysis; SDRIFE: symmetrical drug-related intertriginous and flexural exanthema

IR: immediate readings

DR: delayed readings

Table 3: Recommendations for the application and interpretation of drug patch tests (PTs) (5,16, 18-20, 24,25).

1) Precautions
No skin lesions should be present on the tested skin site(s)
> 1 month after stopping the use of systemic corticosteroids, immunosuppressive drugs, and ultraviolet (UV) exposure
> 1 week after stopping the use of topical corticosteroids on the tested skin site(s)
The skin test site(s) should be kept dry during the entire test period
2) Contraindications
Anaphylaxis to the drug under investigation
3) When To Test
> 4 weeks, and within 1 year, after the disappearance of the drug eruption. Or in DRESS: > 6 months
4) Material for patch testing
Use commercially available patch test preparations, when available (e.g. Chemotechnique, Vellinge, Sweden, or SmartPractice, Calgary, Canada)
OR prepare the material from a commercialized drug: note the trade name and dosage of the drug tested; the capsule sheath (if present) should be moistened, and tested “as is”; reduce tablets to a fine powder, or collect the contents of a capsule, or collect a liquid medicine, and dilute this material to 30% in petrolatum (or alcohol, or water for liquids), and note the final concentration of the active ingredient.
OR dilute the material to achieve a final active ingredient concentration of 10% *
A control patch test could be considered with the vehicle used for dilution of the patch test material (petrolatum, alcohol)
5) Ensure the absence of irritation induced by the patch test material
Check the recommended test concentrations in the literature, and/or test at least 10 negative controls , or retrieve these from the existing literature **
6) Apply the drug patch tests to the skin
Appropriate test chambers, e.g. Finn Chamber on Scanpor 8 mms (Smart Practice), IQ Ultra chamber, IQ ultimate chamber (both Chemotechnique)
On the upper back; in case of fixed drug eruption (FDE) also “in situ”
7) First reading
Occlusion of the patch tests for 2 days. In fixed drug eruption, some authors, recommend occluding the tests for 1 day, whereas others recommend a 2-day occlusion
Remove the patch test material(s), mark the location of the tests with a skin marker, and perform the first reading 30 minutes later.
Report the results (negative [0], IR, doubtful (?+), or positive with erythema and papules (+), erythema, papules and vesicles (++), or erythema, papules, and numerous confluent vesicles/blisters (+++)
8) Second reading
Required on D4, or, if not possible, on D5
For corticosteroids an additional reading should be done at D7
Report the results as mentioned above
9) Determine the relevance of the positive drug patch test(s)
Make sure that the positivity is not due to a contact allergy to any component involved in the preparation, unrelated to the drug eruption

10) In the event of a positive patch test to a commercialized drug
Recover the various components of the drug (active ingredients, excipients) and test them separately, in order to determine whether sensitization occurred to an active ingredient or to an excipient
11) Always remember: a negative patch test does not exclude the responsibility of the tested drug in a cutaneous adverse drug reaction (CADR)

* For pseudoephedrine: start at 1% active ingredient

** Test loratadine at a maximum of 10%, colchicine at 1%, sodium valproate at 1%

Be aware of the presence of sodium lauryl sulfate (SLS), a known skin irritant, in the formulation of certain drugs

Table 4. Concentrations of active ingredients (AI) in drug patch tests (PTs) used for systemic exposure to drugs and their specificities (negative controls) from the literature (mainly Brajon *et al.* [16], and also based on the author's personal experience). The trade names are given for the commercialized ready-to-use products.

ND: not determined, PCF: pure injectable commercialized form.

Drug/Active ingredient	Negative controls	% of AI in the PT	References and/or remarks
<u>ANALGESICS</u>			
<u>NSAIDs</u>			
Acetylsalicylic acid	>100	10.00%	Chemotechnique
Ibuprofen	>100	10.00%	Chemotechnique
Ibuprofen	>10	16.30%	(16)
Diclofenac sodium salt	>20	10.00%	Chemotechnique
Ketoprofen	>20	1.00%	Chemotechnique
Ketoprofen	>20	1.00%	(16)
Metamizole	>20	10%	(22)
Piroxicam	>20	1.00%	Chemotechnique
Celecoxib	>100	1.00%	Chemotechnique
Celecoxib	10	11.45%	(16)
Niflumic acid	>100	2.5%	(16)
<u>non-NSAIDs</u>			
Acetaminophen= paracetamol	>20	10.00%	(16)
Acetaminophen	>20	30.00%	(16)
Nefopam	>10	ND	(16)
Morphine sulfate	10	ND	(16)
Morphine sulfate	10	ND	(16)
Morphine chlorhydrate	>10	10 mg/ml	(16)
Tramadol	>20	9.32%	(16)
<u>ANTI INFECTIOUS DRUGS</u>			
<u>Antibiotics</u>			
<u>Beta-lactams</u>			
Amoxicillin trihydrate	>100	10.00%	Chemotechnique
Amoxicillin	8	25.00%	(16)
Amoxicillin-Clavulanic acid	>100	15.00%	(16)
Ampicillin		5% pet	SmartPractice
Cloxacillin Orbenine 500 mg*	7	27.08%	(16)
Cefalexin	>20	10% pet	Chemotechnique (author experience)
Cefamandole	>100	30.00%	(16)
Cefixime Arrow 200 mg	>100	12.00%	(16)
Cefixime trihydrate	>20	10% pet	Chemotechnique (author experience)
Cefotaxime	>100	30.00%	(16)
Cefotaxim sodium salt	>100	10.00%	Chemotechnique
Cefpodoxime	>100	12.00%	(16)
Cefpodoxime proxetil	ND	10% pet.	Chemotechnique
Cefradine	ND	10% pet	Chemotechnique
Ceftriaxone	>100	30.00%	(16)
Cefuroxime sodium	>20	10% pet	Chemotechnique (author experience)
Clavulanic acid (Potassium clavulanate)	>20	10% pet	Chemotechnique(author experience)
Dicloxacinil sodium salt	>100	10.00%	Chemotechnique
Oxacillin	>100	30.00%	(16)
<u>Cyclins</u>			
Chlortetracycline-HCL		1% pet	SmartPractice

Doxycycline	>10	11.45%	(16)
Doxycycline monohydrate		10% pet	Chemotechnique
Oxytetracycline		3% pet	SmartPractice
Tetracycline-HCL		2% pet	SmartPractice
Fluoroquinolones			
Norfloxacin	>20	10.00%	Chemotechnique
Ciprofloxacin	>20	10.00%	Chemotechnique
Ciprofloxacin	10	18.34%	(16)
Levofloxacin	>20	24.19%	(16)
Pefloxacin	>20	15.38%	(16)
Ofloxacin	>20	15.00%	(16)
Glycopeptides			
Vancomycin	>20	29.27%	(16)
Teicoplanin Targocid 400 mg	>20	30.00%	(16)
Macrolides			
Azithromycin	>20	16.19%	(16)
Clarithromycin	>20	10.00%	(16)
Erythromycin		2% pet	SmartPractice
Erythromycin base	>20	10.00%	Chemotechnique
Josamycin	>20	1.53%	(16)
Roxithromycin	>20	20.27%	(16)
Spiramycin base	>20	10.00%	Chemotechnique (16)
Telithromycin	>20	19.67%	(16)
Other antibiotics			
Clindamycin Dalacine 300 mg	>10	14.40%	(16)
Clindamycin phosphate		10% pet	Chemotechnique
Cotrimoxazole	>20	10.00%	Chemotechnique
Cotrimoxazole	>20	24.00%	(16)
Fusidic acid		2% pet	SmartPractice
Gentamicin sulfate			SmartPractice
Pristinamycin	>20	20.69%	(16)
Pristinamycin	>20	10.00%	Chemotechnique (16)
Rifampicine	>20	24.66%	(16)
Imidazole derivatives			
Metronidazole	>20	21.58%	(16)
Metronidazole		1% pet	SmartPractice
Fluconazole	9	17.65%	(16)
Antiviral agents			
Abacavir	80	10%	23
Ribavirine	>10	20.69%	(16)
Telaprevir	>10	11.11%	(16)
Acyclovir	ND	10% pet	Chemotechnique
ANTICONVULSANTS			
Carbamazepine	>100	1.00%	Chemotechnique (16)
Hydantoin	ND	10% pet	Chemotechnique
Lamotrigine		10% pet	Chemotechnique
Phenobarbitone	10	ND	(19)
Phenytoin	10	ND	(19)
Sodium valproate	10	ND	Could be an irritant even at 1% pet (19)
ANTIEMETIC DRUGS			
Ondansetron	10	9.23%	(16)
	>10	2.42%	(16)
Domperidone	8	3.00%	(16)
ANTIHISTAMINES			
Hydroxyzine	>20	11.54%	(16)
Hydroxyzine hydrochloride		1% pet	Chemotechnique
Levocetirizine	>10	1.47%	(16)

Cetirizine	>10	ND	(16)
Desloratadine	>10	1.42%	(16)
Dexchlorpheniramine	>10	0.85%	(16)
<u>BENZODIAZEPINES</u>			
Tetrazepam	10	7.69%	(16)
Alprazolam	>10	0.06%	(16)
Bromazepam	>10	0.62%	(16)
Diazepam	10	1.79%	(16)
<u>CARDIOVASCULAR DRUGS</u>			
Atenolol	10	7.32%	(16)
Diltiazem hydrochloride		10% pet	Chemotechnique
Captopril		5% pet	Chemotechnique
Perindopril	10	3.26%	(16)
Hydrochlorothiazide	>10	5.36%	(16)
Hydrochlorothiazide		10% pet	Chemotechnique
Amiodarone	>10	17.05%	(16)
<u>CORTICOSTEROIDS</u>			
Budesonide	>100	0.01%	Chemotechnique
Betamethasone	>100	0.12%	(16)
Betamethasone	108	0.22%	(16)
Triamcinolone acetonide	>100	0.10%	Chemotechnique
Tixocortol 21 pivalate	>100	0.10%	Chemotechnique
Dexamethasone 21 phosphate disodium salt	>100	1.00%	(16)
Dexamethasone	>10	ND	(16)
Hydrocortisone	>100	1.00%	(16)
Methylprednisolone	101	0.10%	(16)
Mometasone furoate Nasonex 50 µg	>100	ND	(16)
Bethametasone dipropionate	>10	ND	(16)
Prednisone	>10	0.001%	(16)
Prednisone	7	3.51%	(16)
Prednisolone	>100	1.00%	(16)
Prednisolone	>20	3.51%	(16)
Cortivazol Altim	>10	ND	(16)
<u>HEPARINS AND HEPARINOIDS</u>			
Enoxaparine	>20	PCF	(16)
Nadroparin calcium	>20	PCF	(16)
Calcium heparinate	>20	PCF	(16)
Reviparin-sodium	>20	PCF	(16)
Dalteriparin sodium	>20	PCF	(16)
Heparin	>20	PCF	(16)
Danaparoid	>20	PCF	(16)
Tinzaparine sodium	>20	PCF	(16)
<u>PEG- INTERFERON</u>			
Peg-interferon alpha-2a	>10	PCF	(16)
Peg-interferon alpha-2b	>10	PCF	(16)
Recombinant peg-interferon alpha-2b	>10	PCF	(16)
Recombinant peg-interferon alpha-2a	>10	PCF	(16)
<u>PROTON PUMP INHIBITORS</u>			
Pantoprazole	>20	6.09%	(16)
Esomeprazole	>20	2.92%	(16)
Omeprazole	>20	2.59%	(16°)
Lansoprazole	>10	ND	(16)
Rabeprazole	>10	ND	(16)
<u>OTHER DRUGS</u>			
Allopurinol	>10	16.67%	No value, always negative
Trimebutine	>10	ND	(16)
Trimethylphloroglucinol	7	3.97%	(16)

Table 5 (in the supplementary material): Maximum, non-irritant concentrations for drug prick tests.

Based on literature references and/or on personal experience.

With most other drugs, prick tests can be done with the undiluted commercialized drug.

Name of the drug	Maximum non-irritant concentration	Reference
Antibiotics		
Erythromycin	5 mg/mL	personal experience
Pefloxacin	0.32 mg/mL	personal experience
Spiramycin	37500 IU/mL	personal experience
Neuromuscular blocking agents		
Atracurium	1 mg/mL	(72)
Cisatracurium	2 mg/mL	(72)
Mivacurium	0.2 mg/mL	(72)
Pancuronium	2 mg/mL	(72)
Rocuronium	10 mg/mL	(72)
Vecuronium	4 mg/mL	(72)
Suxamethonium	10 mg/mL	(72)
Opiates		
Alfentanil	0.5 mg/mL	(72)
Fentanyl	0.05 mg/mL	(72)
Morphine	1.0 mg/mL (possibly an irritant)	(72)
Remifentanil	0.05 mg/mL	(72)
Sufentanil	0.005 mg/mL	(72)
Anesthetic agents		
Etomidate	2 mg/mL	(72)
Ketamine	100 mg/mL	(72)
S-ketamine	25 mg/mL (possibly an irritant)	(72)
Midazolam	5 mg/mL	(72)
Propofol	10 mg/mL	(72)
Thiopental	25 mg/mL	(72)
Polyethyleneglycol/macrogol		
PEG 300	undiluted	(72)
PEG 3000	50% water/volume	(36)
PEG 2000	50% water/volume	(36)
PEG 6000	50% water/volume	(36)
Polysorbate 80	20% water/volume	(36)

Table 6 (*in the supplementary material*): **Recommendations for the standardization of drug intradermal tests (IDTs), according to the European Network for Drug Allergy (ENDA)**, adapted from Barbaud et al. (38).

1. Setting and type of drugs: Recommended in a hospital setting under supervision, IDTs must be performed following negative prick tests, using “pharmaceutical grade” drugs for human use in injectable forms. With highly suspected drugs, IDTs are contraindicated in severe cutaneous adverse drug reactions (CADRs).
2. Syringe size and needle gauge: • Tuberculin syringe of preferably 0.5 ml, or, if not available, a volume of 1 ml • Needle gauge of 25, 27 or 30G • Same fixed or a new needle can be used
3. Injection technique - Adopt sterile techniques - Fill the syringe with test solution, change the needle if it is not fixed. Tap the barrel of the syringe to make air bubbles rise to the needle end of the syringe. Expel the air bubbles and excess volume, pushing the plunger to the 0.02 ml mark on the barrel. A syringe with a flat-end plunger is better than a tapered-end to help to measure the volume of the test solution drawn into the syringe. - With the bevel of the needle facing upwards, pierce the skin tangentially in the upper dermis (at an angle of approximately 10° to the skin surface) - Then, slowly inject the measured volume intradermally. Do not inject too fast, as this might be painful.
4. Control: - After the intradermal injection of 0.02 ml of saline or test solution at the recommended concentration for an injection, a wheal measuring 4.5 to 5.5 mm in diameter should form. - If no clear wheal forms, repeat the injection.
5. Record all the injected solutions, batch number and map of the injection sites. Draw around and/or measure the diameter of the immediate injection wheal (Wi). If the wheal is surrounded with ink, always measure the inner diameter.
6. Read the IDTs after 20 minutes. Measure the wheal (W₂₀) <u>and</u> surrounding erythema (E₂₀).
7. If the wheal is not round, measure the length (L), then the width (w) taken

perpendicularly, in the middle of the axis length $W_i = (L+w)/2$.
8. In the patient records and publications, IDT results must be recorded as follows: W_i , W_{20} and E_{20} .
9. At 20 min., the IDT is considered positive only if there is a wheal, $W_{20} \geq W_i + 3 \text{ mm}$ <u>and</u> surrounding erythema, E_{20} .
10. For delayed reactions, read the test at 24 h, 48 h or later (please specify the time interval). IDTs are considered positive when there is an erythematous induration or swelling at the injection site.

Table 7 (in the supplementary material): Maximum concentrations recommended for drug intradermal tests (IDTs).

According to the published literature (mainly Brockow et al. [39] and EAACI position papers [11,50,62]). Additionally, for some drugs, for which we had at least 10 negative controls, values are given from our own personal experience

Drug type	Maximum IDT concentration	References
ANTIBIOTICS		
Beta-lactams		
Amoxicillin, ampicillin and other semi-synthetic penicillins	20 mg/mL	11
Aztreonam	2 mg/mL	11
Benzylpenicilloyl-poly-L-lysine	6 x 10 ⁻⁵ mol/L	11
Benzylpenicilloyl-octa-L-lysine	8.64 x 10 ⁻⁵ mol/L	11
Sodium benzylpenilloate	1.5 x 10 ⁻³ mol/L	11
Benzylpenicillin	10 000 IU/mL	11
Cefepim	2 mg/mL	11
Other cephalosporins except cefepim	20 mg/mL	11
Clavulanic acid	20 mg/mL	11
Imipenem-cilatatin	0.5 mg/mL – 0.5 mg/mL	11
Meropenem	1 mg/mL	11
Quinolones		
Ciprofloxacin	0.006 mg/mL	41,42
Levofloxacin	0.025 mg/mL	41
Ofloxacin	0.05 mg/mL	41
Rifampicin	2 microg/mL	41
Macrolides		
Azithromycine	0.01 mg/mL	41
Clarithromycine	0.05 mg/mL	41
Erythromycine	0.01 to 0.05 mg/mL	41
Rovamycine	37.5 U/mL	Personal experience
Other antibiotics		
Clindamycine	15 mg/mL	41
Cotrimoxazole	0.8 mg/mL	Personal experience
Gentamycin	4 mg/mL	41 (risk of necrosis undetermined)
Rifampicin	0.002 mg/mL	41
Tobramycin	4 mg/mL	41
Vancomycine	0.05 mg/mL	46
Vancomycine	0.005 mg/mL	41
ANESTHETICS		
Neuromuscular blocking agents		

Atracurium	0.01 mg/mL	72
Cisatracurium	0.02 mg/mL	72
Mivacurium	0.002 mg/mL	72
Pancuronium	0.02 mg/mL	72
Rocuronium	0.05 mg/mL	72
Suxamethonium	0.1 mg/mL	72
Vecuronium	0.04 mg/mL	72
Anesthetic agents		
Etomidate	0.2 mg/mL	72
Ketamine	0.1 mg/mL	72
S-Ketamine	0.25 mg/mL	72
Midazolam	0.05 mg/mL	72
Propofol	1 mg/mL	72
Thiopental	2.5 mg/mL	72
Reversal agents		
Sugammadex	10 mg/mL	72
Opiates		
Alfentanil	0.05 mg/mL	72
Fentanyl	0.0005 mg/mL	72
Morphine	0.005 mg/mL	72
Remifentanil	0.005 mg/mL	72
Sufentanil	0.0005 mg/mL	72
Local anesthetics		
Articaine	2 mg/mL	72
Bupivacaine	0.25 mg/mL	72
Chloroprocaine	1 mg/mL	72
Levobupivacaine	0.75 mg/mL	72
Lidocaine	1 mg/mL	72
Mepivacaine	2 mg/mL	72
Prilocaine	2 mg/mL	72
Ropivacaine	1 mg/mL	72
CHEMOTHERAPIES		
Paclitaxel	0.03 mg/mL	Personal experience
Docetaxel	0.1 mg/mL	Personal experience
Platinum salts	1 mg/mL (can induce false-positive results on delayed readings [49])	59,60
Carboplatine	1 mg/mL	39,59,60
Cisplatin	0.1 mg/mL	59,60
Cisplatin	1 mg/mL	39
Oxaliplatin	0.5 mg/mL	59,60
Oxaliplatin	1 mg/mL	39
CORTICOSTEROIDS		
Betamethasone	0.4 mg/mL	54
Cortivazol	2.5 mg/mL	54
Dexamethasone	0.4 mg/mL	54
Hydrocortisone	1 mg/mL	54
Hydrocortisone hemisuccinate	5 mg/mL	53,54

Triamcinolone	4 mg/mL	53,54
Methylprednisolone	4 mg/mL	54
Prednisolone	2.5 mg/mL	54
HEPARINS	1:10 of the usage concentration	39,52
INSULINS	1:10 of the usage concentration	57,58
CYTOKINES, BIOLOGICAL AGENTS		
Anti-TNF		
Adalimumab	50 mg/mL	39,62,64
Etanercept	5 mg/mL	39,62,63,64
Infliximab	2 mg/mL	62,63,64
Infliximab	10 mg/mL	39
Omalizumab	1.25 microg/mL	39
Rituximab	10 mg/mL (7 negative controls)	62,65
Tocilizumab	0.2 mg/mL or 20 mg/mL (10 negative controls) 1.62 mg/mL	66,67
Interferons	usage concentration	68
Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Diclofenac	2.5 mg/mL	Personal experience
Ketoprofen	2 mg/mL	Personal experience
Piroxicam	2 mg/mL	Personal experience
Pyrazolones and other injectable NSAIDs	0.1 mg/mL	39
RADIO CONTRAST MEDIA DERIVATIVES		
Iodinated contrast media	1/10th of the usage concentration for immediate reactions, maybe in pure form for delayed reactions	39,49,50
Gadolinium derivatives	1/10th of the usage concentration	39
PROTON PUMP INHIBITORS		
Esomeprazole	0.4 or 4 mg/mL	47
Omeprazole	0.4 or 4 mg/mL	47
Pantoprazole	0.4 or 4 mg/mL.	47
MISCELLANEOUS DRUGS, EXCIPIENTS, DYES		
Paracetamol (acetaminophen)-	1 mg/mL	Personal experience
Chlorhexidine	0.002 mg/mL (sterile	72

	uncoloured, alcohol-free solution)	
Fluorescein	1/10 th of the usage concentration (10 mg/mL in our experience)	39
Carboxymethylcellulose	0.01 mg/mL	27
Hydroxyethyl starch	6 mg/mL	72
Methylene blue	0.1 mg/mL	72
Patent blue	0.25 mg/mL	72