Patch Testing in Adverse Drug Reactions

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26.1 Introduction

26.1.1 Definition and Types of Cutaneous Adverse Drug Reactions

A CADR is a skin eruption induced by drugs, systemic or topical drugs, used in adequate doses and in the correct indications. CADRs are a frequent problem in Dermatology, but their incidence is not exactly known; 1–5% of inpatients experience such a reaction and it is a frequent cause of consultation in Dermatology [1–5]. Most CADRs are mild, but about 20% can be severe and require hospitalization, for example, in patients with drug hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis which, apart from the skin, have involvement of other organs [5].

Considering its pathomechanism, CADRs can be divided into several types. Most cases belong to type A and C, predictable and chemical, which represent an exaggerated pharmacologic activity of the drug, such as cheilitis from isotretinoin, or xerosis and papulo-pustulo-follicular reactions from inhibitors of epidermal growth factor receptor [6]. They can be enhanced by modification of drug bioavailability due to drug interactions, reduced metabolization, or elimination, especially in genetically susceptible individuals. Type D includes late (delayed) reactions, such as teratogenesis or carcinogenesis, and type E results from end-of-dose reactions [7]. Type B reactions are idiosyncratic, unexpected, unpredictable, and among these, many are due to immune reactions induced by the drug [5] (Table 26.1).

J.D. Johansen et al. (eds.), *Contact Dermatitis*,
DOI: 10.1007/978-3-642-03827-3_26, © Springer-Verlag Berlin Heidelberg 2010

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Table 26.1 Main types of adverse drug reactions, according to its mechanism [7]

Type of adverse reaction	Mechanisms
A – Augmented	Exaggerated pharmacologic activity of the drug
B – Bizarre[a]	Idiosyncratic, unpredictable, usually immune-mediated
C – Chemical	Chemical or pharmacological effect of drug
D – Delayed	Reactions occurring late, related mainly with carcinogenesis or teratogenesis
E – End-of-doses	Reaction to drug suspension

[a]These are the ones that will be dealt with in this chapter

26.1.2 Main Clinical Patterns of Immune-Mediated CADRs

Systemic exposure to drugs can sensitize the individual and lead to a wide variety of CADRs or drug eruptions. Some reactions are not specifically induced by a drug, such as a maculopapular exanthema, urticaria or angioedema, lichenoid reaction, or subacute lupus erythematosus. Other patterns are almost exclusively induced by drugs (>90%), such as Stevens–Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, and acute generalized exanthematous pustulosis [5, 8].

According to their time course, drug eruptions can be divided into immediate reactions, occurring within minutes to 1–2 h of drug intake, and delayed reactions that occur several hours, days or up to 6 weeks after drug exposure. Immediate reactions present as urticaria, angioedema, or anaphylaxis, whereas for delayed reactions the clinical spectrum is much wider: maculopapular eruptions (the most frequent reaction pattern) (Fig. 26.1), exfoliative erythroderma, acute generalized exanthematous pustulosis (Fig. 26.2), localized fixed drug eruptions, Stevens–Johnson syndrome (Fig. 26.3), toxic epidermal necrolysis (Fig. 26.4), other bullous reactions mimicking pemphigus vulgaris or bullous pemphigoid, vasculitis, and lupus erythematosus [9].

Topically applied drugs may cause contact dermatitis reactions or photosensitive contact dermatitis. Topical sensitization and subsequent systemic exposure may induce skin reactions similar to systemic drug eruptions (maculopapular exanthema) [10] or patterns more typical of a systemic contact dermatitis, such as acrovesicular dermatitis, the "baboon syndrome" (see Chap. 17), or Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) [11, 12]. It is clear that in these situations patch testing can be of great help as a diagnostic tool [11].

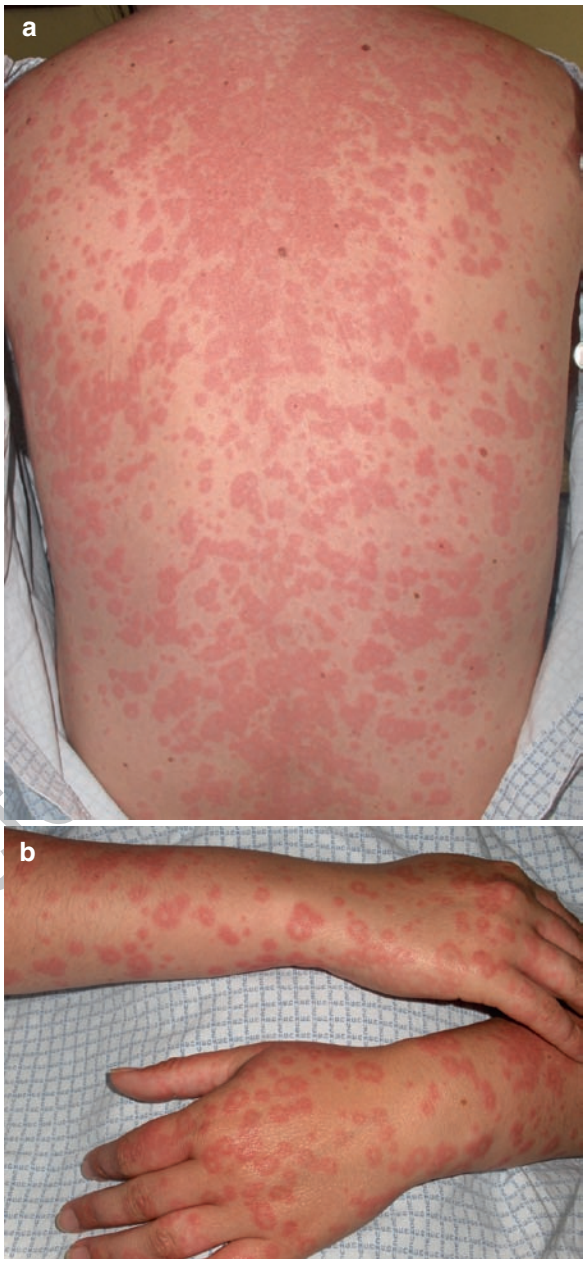

Fig. 26.1 Generalized maculopapular exanthema from amoxicillin that developed on the ninth day of therapy, with symmetric lesions on the trunk (**a**) and targetoid lesions on the hands and forearms (**b**). This patient had positive patch tests with amoxicillin and ampicillin at 1 and 10% pet. and negative tests with penicillin G, dicloxacillin, and several cefalosporins

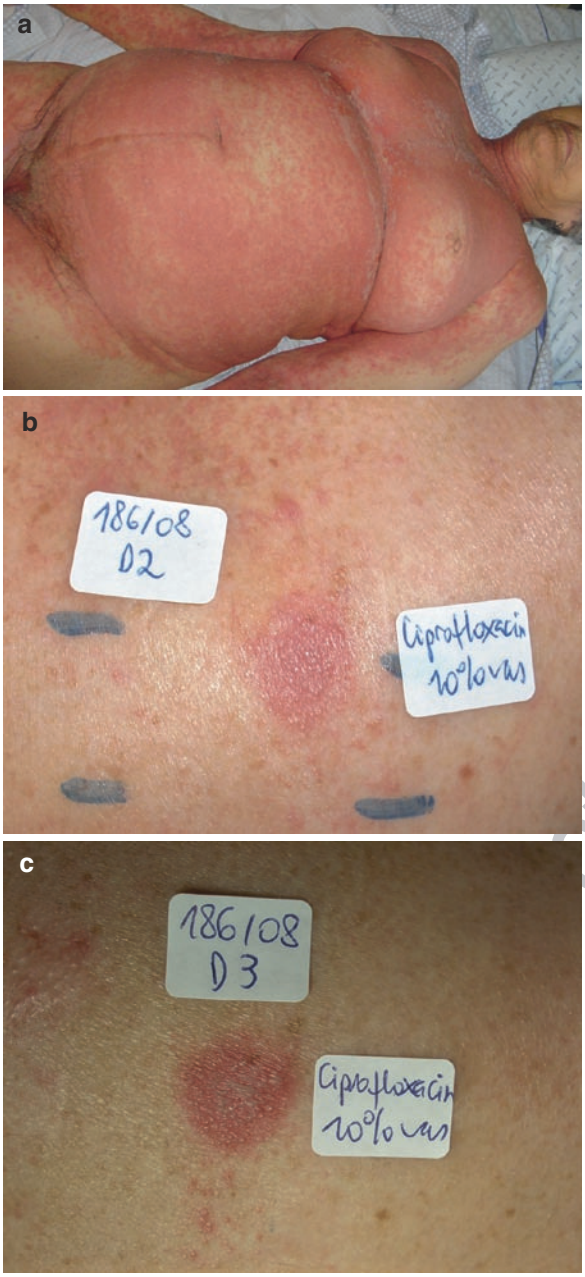

Fig. 26.2 Acute generalized exanthematous pustulosis from ciprofloxacin, on the third day of evolution, with coalescent pustules on erythema, predominating on the main body folds (**a**). Patch tests were positive with ciprofloxacin at 10% pet. and also norfloxacin and lomefloxacin. The erythemato-vesicular reaction at D2 (**b**) changed into a pustular reaction at D3 (**c**). Histopathology showed an intraepidermal spongiform pustule as in the acute eruption

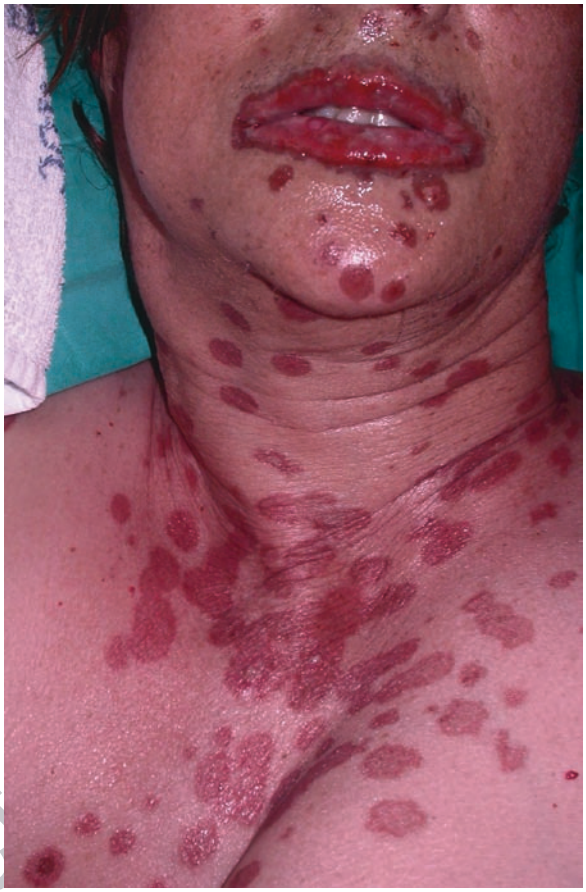

Fig. 26.3 Stevens–Johnson syndrome from lamotrigine, an antiepileptic drug frequently responsible for this clinical reaction pattern, particularly in children. Note the typical oral involvement, with erosion of the whole semimucosa of the lower lip

In patients with drug eruptions without previous contact sensitization, patch testing can also induce specific positive reactions, but the sensitivity of this test is much lower than in allergic contact dermatitis [13, 14]. The value of patch testing in CADRs has not always been appreciated, but there is growing interest in this field. It is a safe method and results can be very rewarding, as positive test results can be very useful to confirm drug imputability established on clinical grounds. Patch testing can also be helpful for studying cross-reactions and understanding pathomechanisms involved in drug eruptions [15].

Core Message

› Drug eruptions are adverse skin reactions caused by a drug used in normal doses. They present with a very wide variety of clinical patterns.

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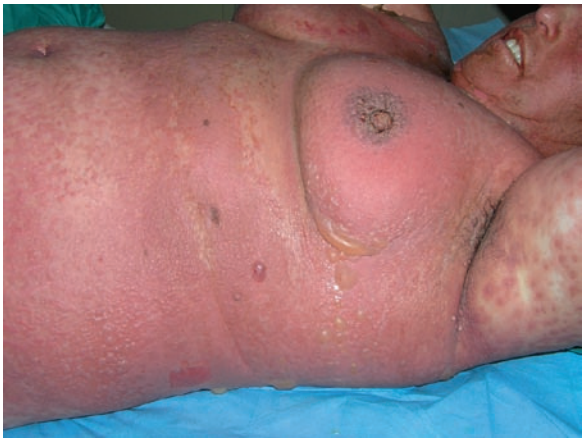

Fig. 26.4 Toxic epidermal necrolysis/Lyell's syndrome induced by carbamazepine. Note confluent flaccid bullae on the trunk, already with a few areas of epidermal detachment, and atypical target lesions in the arms. Although this is not frequent, this patient had positive patch tests to carbamazepine, which on histology had skin apoptosis of the whole epidermis, such as in the acute eruption of the toxic epidermal necrolysis

26.1.3 Pathomechanisms Involved in Immune-Mediated Drug Eruptions

In most CADRs of the type B there is involvement of the immune system. Either antibodies or T-cells with their specific receptor recognize the drug, or a metabolite, or any of these combined with a peptide or with an autologous cell. These drug reactions can be classified according to the immunological reaction types of Gell and Coombs (see Chap. 3), but often it is not one isolated immunological mechanism that is responsible for the event: combinations of type I and IV hypersensitivity exist [16] and even more complex mechanisms can be involved [5, 17]. Genetic susceptibility is also important, as in cases of toxic epidermal necrolysis and Stevens–Johnson syndrome from allopurinol and carbamazepine and, particularly, in abacavir hypersensitivity syndrome, where HLA-B*5701 pretesting has significantly reduced this severe adverse reaction [18, 19].

Immediate reactions involve mainly drug-specific IgE and mast cell and basophil degranulation [20], whereas delayed reactions after systemic drug exposure depend mainly on type IV hypersensitivity reactions, with previous T-cell sensitization [21, 22]. By the clinical pattern and time course, we can suspect which mechanisms can be involved, but sometimes it is not possible [23].

The pseudo-allergic (anaphylactoid) reactions, including urticaria induced by acetylsalycilic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) and angioedema induced by angiotensin conversing enzyme inhibitors (ACEi), are examples of nonimmunological reactions mimicking a true (type I) allergic reaction. The most plausible explanation for these reactions is a nonspecific release of histamine and other mast cell and basophil mediators without the participation of IgEs or a reduced capacity to metabolize kinins, with consequent accumulation of the potent vasodilator bradykinin [24].

26.1.4 T-Cell Involvement in Drug Eruptions

Apart from allergic contact dermatitis and systemic contact dermatitis, delayed type IV hypersensitivity has been documented in maculopapular exanthema, in drug hypersensitivity syndrome/DRESS, in acute generalized exanthematous pustulosis, in the localized fixed drug eruption, and in the more extended bullous reactions in a continuum from Stevens–Johnson syndrome to toxic epidermal necrolysis [9]. These reactions usually begin within 7–21 days on the first exposure, but rechallenge is usually accelerated, positive with lower dose and more severe, suggesting specific immune sensitization. In the skin biopsies of the CADR there is mainly a dermo-epidemal infiltration of activated T-cells, some of which specifically recognize the drug or one of its metabolites. And, apart from the skin, drug-specific T-cells have been isolated from the blood or blister fluid during the acute reaction and also, later, from skin biopsies of positive patch tests [9, 25–28]. As previously referred, the clinical presentation of these CADRs is very heterogeneous, even though there are data to support the involvement of delayed type hypersensitivity mechanisms [5]. Apart from other individual circumstances, this heterogeneity very probably depends on different pathways of drug recognition by the immune system and on the subtypes of effector T-cells. Although there is little knowledge on which cells participate in the process of drug presentation during the sensitization phase, the drug, a metabolite or both, can be recognized by the TCR combined with HLA molecules, either class I, class II, or both, with or without previous processing by the antigen presenting

cell [29]. There are many studies on the effector T-cells (Th1, Th2, Tcit) and on the main cytokines and chemokines involved in the final reaction (IFN-gama, IL-8, IL-5, eotaxin, TNF-alfa, Fas) [22, 30]. Recently, subtypes of type IV hypersensitivity have been defined in the participation of CADR [22, 31]. A Th1 pattern with IFN-gama production, considered a type IVa hypersensitivity, is mainly involved in allergic contact dermatitis and maculopapular exanthema. Type IVb involves mainly a Th2 response, with IL-5 and eotaxin production and, consequently, eosinophil recruitment and activation. Actually, there is eosinophil infiltration in the dermis in maculopapular exanthema, and systemic eosinophilia is one of the criteria for drug hypersensitivity syndrome/DRESS [17, 32, 33]. In acute generalized exanthematous pustulosis, T-cells isolated from the blood and the skin produce high amounts of the chemokine CXCL8 (IL-8) and GM-CSF, with consequent preferential neutrophil recruitment that is responsible for the epidermal spongiform pustule typical of this CADR (type IVd hypersensitivity) [34, 35]. Type IVc, with predominant T-cell cytotoxic activity, is involved at a lower level in maculopapular exanthems, but is very pronounced in Stevens–Johnson syndrome and toxic epidermal necrolysis, where keratinocyte apoptosis is the hallmark of the reaction [22, 36, 37]. Fixed drug eruptions are also typical T-cell-mediated reactions, with a special localization pattern and a very particular retention of drug-specific T-cells in lesional areas. These resting T-cells are activated very shortly after topical or systemic drug exposure, and produce high amounts of IFN-gama and cytotoxic mediators (TNF-alfa and Fas), but precocious infiltration of regulatory T-cells (Tregs) seems to prevent its evolution to the more severe bullous reactions [38, 39]. Delayed type hypersensitivity is also involved in some photosensitive drug reactions, mainly in those with an eczematous pattern [40–42].

Therefore, the participation of drug-specific T-cells in several drug eruptions other than allergic contact dermatitis makes patch testing suitable for their study. Nevertheless, the rate of negative reactions is much higher, as mechanisms other than T-cell-derived hypersensitivity are involved, often in a more complex interplay with other systemic inflammatory reactions (viral infections, autoimmune diseases). Also in some CADRs, very probably, the allergen is not the drug itself, but a systemic metabolite and, although skin metabolism is quite efficient, some drugs are not metabolized by skin cells [43]. And there are certainly other reasons, not completely understood, to explain many negative patch tests.

Core Message

› Many delayed drug eruptions are T-cell-mediated and, therefore, patch testing can be adequate in their study.

26.2 The Workup in the Diagnosis of an Immune-Mediated CADR

26.2.1 Clinical Diagnosis and Drug Imputation

The diagnosis of a drug eruption is easier if we are facing a clinical pattern typical of a CADR, such as a fixed drug eruption, a toxic epidermal necrolysis, or a generalized exanthematous pustulosis. In nonspecific skin reactions patterns, a particular workup has to be done to exclude other causes for the rash, such as a viral infection in maculopapular exanthema or a non-drug allergen in acute urticaria or angioedema. In these situations, the diagnosis of drug eruption can be a diagnosis of exclusion.

In severe CADR, such as toxic epidermal necrolysis, DRESS, and acute generalized exanthematous pustulosis, complementary tests are needed to evaluate the degree of systemic involvement.

At the time of diagnosis, it is extremely important to identify the culprit drug. In most CADRs, improvement depends on the drug suspension and prognosis depends mainly on an early drug withdrawal.

Imputation of the culprit drug is performed mainly on clinical grounds, based on extrinsic and intrinsic criteria. Extrinsic criteria include all previous reports of such a CADR. Intrinsic criteria are mainly based on the chronology and clinical characteristics of the adverse event: the clinical pattern of the eruption, its chronological relation with the initiation and suspension of the drug, and information on previous drug exposure, with or without reaction (accidental rechallenge) [44, 45]. No single complementary test can replace a good characterization of these parameters.

Table 26.2 Main CADRs and the most adequate skin test according to each clinical pattern

CADR pattern	Expected free interval	Most adequate test to perform	
		In vivo	In vitro
Urticaria/angioedema anaphyalxis	Minutes to 1 h	Prick, i.d.[a] Oral challenge[b]	IgE (RAST/CAP) Basophil activation
Maculopapular exanthema	7–21 days 2 days[c]	Patch, i.d.[a] Oral challenge	LST/LTT
Drug hypersensitivity/DRESS	3–6 weeks	Patch i.d.[d]	LST/LTT[e]
Acute generalized exanthematic pustulosis	2–3 days	Patch	LST/LTT
Stevens–Johnson syndrome Toxic epidermal necrolysis	7–21 days 2 days[c]	Patch	LST/LTT
Fixed drug eruption	6–24 h	Lesional testing	
Systemic photosensitivity	2 days	Photopatch test Oral photoprovocation	

[a]Perform i.d. tests only if prick or patch tests are negative

[b]Not adequate in cases of anaphylaxis or severe angioedema

[c]On drug reintroduction

[d]i.d. is not advised, on a first basis, due to a possible severe reaction

[e]LST/LTT (lymphocyte stimulation or transformation tests) are often negative during the acute phase of DRESS

But, even in the cases where very accurate data are available, the imputability or causality index for a single drug can be very low: many patients who develop a CADR are on multiple drugs; any drug can induce a drug eruption; different drugs can induce the same clinical pattern of drug eruption; and, the interval between drug initiation and development of the CADR can vary widely (6 h up to 6 weeks), even considering only delayed reactions (Table 26.2).

26.2.2 Complementary Tests to Confirm Drug Imputation

Drug reintroduction is considered the more definitive test for confirming the culprit drug, but it does not always reproduce the skin reaction [45, 46]; it is time-consuming when several drugs are suspected and it is contraindicated in severe reactions, such as toxic epidermal necrolysis or drug hypersensitivity syndrome/DRESS [45]. Therefore, complementary clinical and laboratory investigations have to be conducted in order to try to confirm, or deny, an imputable drug.

Laboratory tests, such as specific IgE or basophil activation, are used for the study of immediate reactions, and lymphocyte transformation tests (LTT) or lymphocyte stimulation tests (LST) are used for studying mainly delayed hypersensitivity reactions [47]. They can help in the diagnosis, with the advantage of being an in vitro method that, in some circumstances, can be performed during the acute phase. Nevertheless, these tests are not available for most drugs, procedures are not standardized, results are inconsistent with undetermined sensitivity and specificity, and therefore, they are not performed on a routine basis [23, 47].

Skin testing can be used later, after the resolution of the CADR. It is important to choose the most adequate skin test, according to the reaction pattern, even though this is not always so straight. (Table 26.2) Tests with immediate readings, such as prick, scratch, or intradermal (i.d.) tests, are advised for immediate reactions such as urticaria and angioedema, whereas tests with delayed readings, such as the patch test, are mainly recommended for delayed skin reactions, e.g., eczematous reactions, maculopapular exanthema, erythroderma, drug hypersensitivity syndrome/DRESS, acute generalized exanthematous pustulosis, fixed drug eruption, Stevens–Johnson syndrome, and toxic epidermal necrolysis [15, 48]. Prick and i.d. tests with late readings, performed when patch tests are negative, may increase the effectiveness of skin testing. In two

separate studies these tests improved the diagnosis by about 10% in nonimmediate reactions from aminopenicillins and synergistins [49, 50]. Commercial material for i.d. testing is not available for most drugs and, therefore, it has to be prepared, on a patient basis, in a sterilized setting, which is not always feasible. Moreover, in case of positive results, it may be difficult to use controls to evaluate the specificity of the reaction, Also, it is recommended to perform i.d. testing in a hospital setting, particularly in the study of severe CADRs [51].

When positive, in vitro or in vivo tests can be of help in confirming which drug was responsible for the CADR, but, on the contrary, these tests are very seldom able to exclude the involvement of a drug.

26.3 Patch Testing in CADRs

26.3.1 The General Value of Patch Testing

Patch testing in the study of drug eruptions has been performed for many years, but not as a systematic investigation in large multicenter investigational studies. There are a few studies with a relative large number of patients patch tested with drugs [13, 51, 52] and they include a wide variety of patterns of drug eruptions. Nevertheless, the inclusion criteria are quite different and the imputability/causality index for the drugs studied (very probable/probable/possible) is not known in most cases. Also, as there are so many patterns and so many responsible drugs, it is difficult to ascertain the patch test reactivity and its real value (sensitivity and negative predicative value) in the many different settings.

While considering a wide range of drug eruptions, the frequency of positive tests varies from 7.5 to 54% [13, 14, 51–54]. Apart from patient selection, patch test reactivity depends mainly on the clinical pattern of the drug eruption and the drugs involved [51–54].

Patch tests are mostly positive in eczematous eruptions, systemic contact dermatitis, maculopapular, and erythrodema, and particularly, in more severe reactions [12, 14, 20, 51, 53, 55] (Table. 26.3).

In acute generalized exanthematous pustulosis there are many reports with positive patch tests, but with a few cases each [8, 26, 34, 35, 55–59]. In their study, Wolkenstein et al. found 50% of positive tests (7+out of the 14 patients tested) [60]. In this CADR, patch tests can show a pustular reaction with an epidermal spongiform pustule on skin biopsy, as in the acute reaction [26, 35, 56, 61] (Fig. 26.2b, c).

Table 26.3 Patch test results according to the type of eruption (adapted from Osawa et al. [52] Barbaud et al. [51] and Lamminatausta and Kortekangas-Savolainen [13])

CADR pattern	Number positive tests/number patients tested (%)			
	Osawa et al. [52] ($n=197$)	Barbaud et al. [51] ($n=72$)	Lammintausta et al. [13] ($n=826$)	Other studies
Maculopapular	10/72 (14)	16/27 (59)	81/785 (10.3)	33/61 (54) [14]
Erythroderma	8/15 (53)	5/7 (71)		
Eczematous	9/17 (53)	3/9 (33)		
Erythema multiforme	6/29 (21)			
Lichenoid	2/11 (18)			
Photosensitivity		4/4[a] (100)	2/12 (16.7)	
Fixed eruptions	2/6 (33)	0/3	8/28 (28.6)	26/30 (87) [68]
Urticaria/angioedema		2/18 (11)		
AGEP				7/14 (50) [60]
SJS/TEN				2/22 (9) [60]
Miscellaneous	15/47 (32)	1/6[b] (17)		
Total	62/197 (31)	31/72 (43)	101/826 (12.2)	

[a]Photopatch test

[b]Positive test in acute generalized exanthematous pustulosis

In DRESS, patch tests are often positive with abacavir [19, 62, 63] and antiepileptics, particularly carbamazepine [17, 64, 65] (Fig. 26.5). Patch test reactivity is much lower, below 10%, in Stevens–Johnson syndrome or toxic epidermal necrolysis [55, 60]. In some occasions histopathology of the patch test can also reproduce the full thickness epidermal apoptosis, such as in the acute reaction.

Fixed drug eruptions are unique in the persistence of drug-specific T-cells in residual skin lesions, so we can expect to find positive tests on the these lesions, in a high percentage of cases [66–68], particularly, in fixed drug eruptions from NSAIDs [66, 69, 70] (Fig. 26.6). Alanko found as many as 26 positive tests out of 30 (87%) [68].

In photosensitive eruptions, when it is not a clearly phototoxic reaction, photopatch tests can be rewarding in the study of systemic photosensitivity as in photoallergic contact dermatitis [41, 42, 71, 72]. Piroxicam [40, 73–77], ketoprofen [71, 78], the fluorquinolones [42, 79, 80], and flutamide [81, 82] are examples of drugs that frequently elicit positive photopatch tests.

The reactivity of patch testing also depends on the culprit drug. Carbamazepine induces positive patch tests in more than 70% of the cases of delayed drug eruptions [51, 65, 83–86] (Fig. 26.5). High reactivity is also observed with tetrazepam [35, 51, 87–89], abacavir [19, 62, 63, 90], aminopenicillins [13, 20, 91], cefalosporins [13, 92], synergistines [50], cotrimoxazole [14]

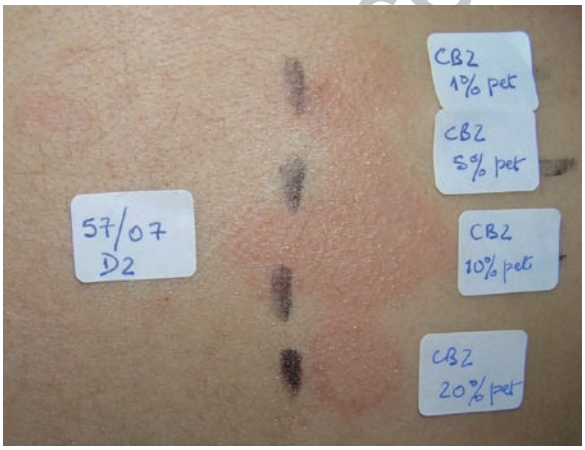

Fig. 26.5 Positive reactions to carbamazepine tested at several concentrations (1–20% pet) in a patient with a severe exanthema in the context of a DRESS (drug reaction with eosinophilia and systemic symptoms). In this severe drug reaction it is advised to test carbamazepine only at 1% pet

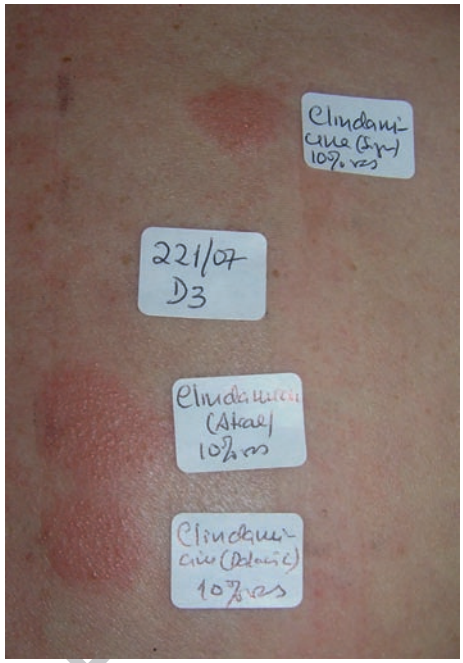

Fig. 26.6 Lesional testing in a residual pigmented lesion of fixed drug eruption. Positive reaction with the NSAID, nimesulide, tested at 1% pet, presenting as erythema and infiltration. Note the negative reaction to another NSAID, tested at the *left* side, confirming the specific nature of the reaction

clindamycin [13, 93–95], (Fig. 26.7) diltiazem [14, 96–98], heparin derivatives [14, 99, 100], corticosteroids [101–103], pseudoephedrine [104], and hydroxyzine [14, 105, 106]. Nevertheless, contrary to the most regularly referred rate of 30–40% of positive reactions to betalactam antibiotics [51], in a recent review by Blanca et al., the rate of positive reactions was much lower (2.6%) [20], which is probably due to a different patient selection (Table 26.4).

The list of drugs reported to elicit positive patch or photopatch test reactions is increasing every day, as this method is increasingly being used in the diagnosis of drug eruptions.

Core Message

› Patch tests are more frequently positive in maculopapular exanthema, acute generalized exanthematous pustulosis, and fixed drug eruptions.

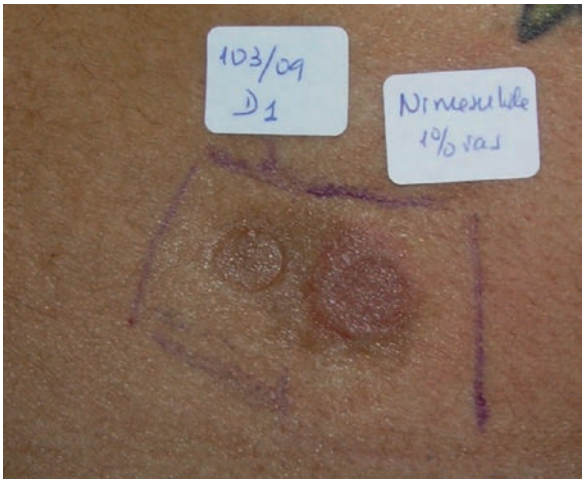

Fig. 26.7 Positive patch tests with clindamycin, the pure substance tested at 10% in pet.(*upper test*), with identical results when testing with the smashed content of the pills of clindamycin from two different brands (Dalacin C® and Clindamicina Atral®), both prepared at 10% in pet (*lower reactions*)

26.3.2 Patch Test Technique

It can take weeks before skin reactivity can be evaluated properly by patch testing. Thus, it is advisable to wait several weeks after the rash has gone to perform patch tests. It is not known exactly how long, but 6 weeks after complete resolution of the CADR is usually advised [15, 107]. Also, we do not know for how long skin sensitivity persists. Although some reactions are lost, many patients tested after 10 years still react positively [49]. Therefore, it is usually recommended to patch test within 6 weeks to 6 months [15].

Patch testing is performed in the generally accepted way on the back, as in the study of allergic contact dermatitis. In particular cases, as in fixed eruptions, reactivity occurs only in skin areas where the skin reaction has occurred [66, 108, 109]. The application time is usually 2 days, but occasionally it can be convenient to remove tests at D1 [49]. Readings are performed at D2 and at D3 or D4, and scored negative to 3+, according to the ICDRG guidelines.

In fixed drug eruptions, test materials are applied in duplicate: on an inactive, residual lesion and on the normal back skin, which serves as a negative control. The residual pigmentation is a useful marker to indicate the area to apply the test. Tests are usually applied for 1 day, with occlusion, as in patch testing. Readings are performed at D1 and D2, or at D3 if previously negative [66]. As sometimes positive reactions are seen only in the first 24 h, Alanko [68] prefers an open test, which makes observations possible during this period.

Table 26.4 Patch test results in delayed CADR, according to the culprit drug

Culprit drug	Number positive reactions/number of patients tested (%)		
Betalactam antibiotics	4/24 (29) [53]		
Amoxicillin	10/247 (4) [13]	7/17 (41.2) [51]	
Cefalosporins	12/220 (4.1%) [13]		
Pristinamycin	7/8(87) [51]	17/20 (85) [13]	
Trimethoprim	10/163 (6.2%) [13]		
Cotrimoxazole	4/140 (2.9) [13]		
Clindamycin	12/63(19) [13]	5/33 (15) [94]	8/26 (31)[a]
Aciclovir	2/8(25) [45]		
Abacavir			7 [63][b]
Carbamazepine	6+/7 (86) [53]	13/17 [64]	
Diltiazem	3/9(33.3) [13]	7/13 (54) [98]	
Allopurinol	1/10 (10) [13]	0/19 [64]	
Pseudoephedrine	5/16 (31.2) [13]		
Piroxicam (Photo)	75/82 (91.4) [73]		

[a]Personal data
[b]One study with seven positive patch tests [63]

A reaction is regarded as positive, if it occurs only in the residual lesion, and when clear erythema is visible for at least 6 h. Often there is erythema with infiltration (Fig. 26.6), eczema, or a bullous reaction that mimics the histopathology and clinical pattern of the acute fixed drug eruption [66, 70]. The reaction occurs exclusively in the area of application of the test or reactivation of the whole residual lesion can occur [66].

In systemic drug photosensitivity photoepicutaneous patch tests are performed, as in photoallergic contact dermatitis, using mainly UVA irradiation, at a dose of 5 J/cm^2 [41, 110, 111] (see Chap. 29).

26.3.3 Material for Patch Testing with Drugs

26.3.3.1 Patch Testing with Pure Drugs

In recent years, with the increasing interest in patch testing in drug eruptions, several firms that prepare allergens for the study of contact allergy are also producing standardized drug allergens with the pure active products. Of course, there is only a very limited number of drug allergens and every drug can induce a CADR. Nevertheless, the list includes drugs more frequently responsible for delayed CADRs: antibiotics, antiepileptic, NSAIDs, and some isolated drugs (Table 26.5). No controls are needed for these allergens, as many patients, who have been exposed to the drug with no reaction and, also nondrug exposed subjects, have been tested with no reaction.

This makes patch testing with drugs simple, allows testing several drugs at the same time and, particularly, testing with analogous chemicals to study cross-reactions and find possible replacement drugs. Actually, these studies have shown very interesting data on patterns of cross-reactivity that may be very informative for the patient and the doctor.

But, these commercialized drug allergens might be improved, as it is not known yet if the most correct concentrations or the most adequate vehicles are being used. Recommended concentrations are usually between 1 and 20% of the pure chemical, doses that are usually higher than in the study of allergic contact dermatitis. But for drugs, such as carbamazepine, low concentration, 1% or even below, can be enough [86, 112] (Fig. 26.5). Increasing concentration above 1 or 5% pet. does not always increase patch test reactivity, as shown for carbamazepine and amoxicillin [49, 112]. For the 20% concentration, carbamazepine, hydrochlorotiazide, propanolol, sulphametoxazol, and thrimetoprim did not evoke reactions either when tested in 200 volunteers [1], or in previously exposed patients [65]. Although reactivation of the CADR during patch testing is exceptional [65] [144], in the case of a severe drug eruption, it is advisable to start with lower concentrations [15].

Also, there is not enough data on the best vehicle to perform patch testing. Most chemicals react when prepared in petrolatum, but in some cases water, ethanol, or acetone may be more adequate, as in the case of estradiol [10], or DMSO may be necessary to solubilize cotrimoxazole and its constituents [55, 113].

26.3.3.2 Patch Testing with Drugs Used by the Patient

If the pure drug is not available, which is often the case, patch testing can be done with the drug used by the patient, either a tablet, a capsule, or the solution for oral, i.v., or i.m. use. The amount of active drug in a tablet varies and can be very low. Therefore, it is preferable to use the content of a capsule or the powder for parenteral use, which usually have more active drug. This powder, or the fine powder obtained from smashing the pill after removing the external coating, can be diluted in petrolatum and water, or other vehicles, in a way to have the active drug in the final concentration at 10% (Fig. 26.7). If the concentration of the active drug is too low, it is recommended to prepare the smashed powder of the pill at 30% [15]. Of course, in this method, the final concentration of the active drug can vary a lot, but 30% is the highest concentration to obtain a homogenous preparation [15].

When tests are positive with these preparations, it is recommended to have serial dilutions and it is obligatory to test, at least, ten controls, preferably previously exposed individuals who have given their informed consent.

Even when tests have been done with pure chemicals, it can also be worthwhile to perform tests with the filler materials and the original drug preparation. In principle, reactions to the "inert" filler substances and additives are possible, but in practice they are rare [114–117].

Table 26.5 Commercially available drug allergens for patch testing

Group of drugs	Drug allergen	Concentration vehicle (% pet)	Company
Antibiotics	Penicillin G, potassium salt	10	CD
	Ampicillin	5	MT
	Amoxicillin trihydrate	10	CD
	Dicloxacillin sodium salt hydrate	10	CD
	Cefradine	10	CD
	Cefalexin	10	CD
	Cefotaxim sodium salt	10	CD
	Doxycyclin monohydrate	10	CD
	Minocycline hydrochloride	10	CD
	Erythromycin base	10	CD MT
	Spiramycin base	10	CD
	Clarithromycin	10	CD
	Pristinamycin	10	CD
	Cotrimoxazole	10	CD
	Norfloxacine	10	CD
	Ciprofloxacine hydrochloride	10	CD
	Clindamycin phosphate	10	CD
Antiepileptics	Carbamazepine	1	CD
	Hydantoin	10	CD
NSAIDs	Acetylsalicylic acid	10	CD MT
	Diclofenac sodium salt	1	CD Bi MT
	Ketoprofen	1	CD Bi Mt
	Naproxen	5	Bi MT
	Piroxicam	1	CD Bi MT
	Acetaminophen	10	CD Bi
	Ibuprofen	10	CD Bi MT
Miscellaneous	Acyclovir	10	CD
	Hydrochlorothiazide	1 and 10	CD
	Diltiazem hydrochloride	10	CD
	Captopril	5[a]	CD

CD chemotechnique diagnostics, Malmö Sweden

MT Martí Tor, Dermatitis de Contacto, Barcelona, Spain

Bi Bial Aristégui, Bilbao, Spain

[a]Doubtful reactions may occur with this concentration

26.3.4 Safety of Patch Testing

The risk of reactivation of the drug eruption is very low [14, 118], even in serious delayed CADRs [64], but it has been occasionally reported with acyclovir, pseudoephedrin, pristinamycin [51], and carbamazepine, particularly when testing with the powder of the pills [119].

Serious immediate reactions evoked by patch testing are rare and have been described mainly in the study of anaphylaxis [120–122], particularly with penicillins, neomycin, or bacitracin. For safety reasons, it is practical to observe the patient for approximately half an hour after application of the test material.

The risk of patch testing is considerably lower compared with i.d. tests. Thus, the patch test is a good test to start with. If negative and, for the particular patient, it is important to prove the causality of the drug, the study can continue with the sequential use of prick, scratch, and i.d. tests with a delayed reading [15]. If all are negative, as a next step, a provocation test can be performed in a hospital setting, except if there is a contraindication, namely, a previous severe reaction, such as DRESS or toxic epidermal necrolysis, or the involvement of drugs as antiepileptics or salazosulfapyridine [45].

Another adverse patch test effect is sensitization by patch testing; this is rarely seen, even with penicillins [123].

26.3.5 Specificity of Patch Test Reactions

Positive patch test reactions, performed according to the recommendations [15], have been shown to be highly specific. Histopathology of drug patch tests is often analogous to the acute reaction [61, 124] and some T-cells that infiltrate the skin, in the patch test, specifically recognize the drug [25–28, 34]. Actually, drug-specific T-cells, with phenotypic and functional characteristics similar to those isolated from the blood or the skin during the acute phase of the CADR, have been isolated from positive patch tests with several drugs, such as amoxicillin, carbamazepine, lamotrigine, sulfonamides, fluorquinoles, and tetrazepam [25–28, 34, 35].

Patch testing with pure drugs or with low concentrations of the commercial products rarely yields false positive reactions. But, occasionally, constituents of the excipient of the commercial drug can cause false positive reactions due to irritation or low pH or they can induce a nonrelevant positive patch test reaction in a previously contact sensitized patient [114]. For instance, false positive results have been observed with the powder of the pills of spironolactone (Aldactone®), colchicine, captopril (Lopril®), cloroquine (Nivaquine®), celecoxib (Celebrex®) tested at 30% pet, and with omeprazole (Mopral®) tested at 30% aq. [14, 55, 114].

False-negative reactions can be expected due to technical problems of the patch tests (low concentration or wrong vehicle, deficient skin penetration, wrong timing for performing patch testing), but there are certainly many other explanations for the absence of skin reactivity on patch testing: the responsible hapten is a drug metabolite that is not formed in the skin, the CADR is not an immune reaction or not dependent on the delayed hypersensitivity or, apart from drug exposure, concomitant factors (viral infection or concomitant drugs) are necessary for enhancing drug hypersensitivity [91].

For cotrimoxazol and acyclovir, patch tests in petrolatum are often negative, and DMSO or other penetration enhancers may be necessary to have positive patch tests. There is, for the moment, no explanation for the negative patch tests to allopurinol in delayed CADRs, presumed to be immune-mediated, even when there is a positive accidental rechallenge. Although there is one report of a positive test in the study by Lammintausta and KorteKangas-Savolainen [13], in our experience, with more than 30 patients now, we did not observe a positive patch test with allopurinol, using low or high concentrations (1–20%), petrolatum or ethanol as excipient, with or without tape stripping, or even using one of its metabolites (8-oxypurinol) in different concentrations and vehicles [125].

26.3.6 Evaluating Cross-Reactivity on Patch Testing

Cross-reactivity observed among drugs in CADRs can be studied, sometimes with very interesting results, at the patch test level.

It has been shown, in maculopapular exanthema, that amoxicillin and ampicillin always cross-react [54, 112], and this cross-reactivity is neither often extensive to benzilpenicillin or carbopenens [20], nor to cefalosporins except, eventually, cefalexin [126]. A similar pattern is usually confirmed by oral challenge [20, 49]. There is also frequent cross-reactivity among the cefalosporins

and the fluorquinolones [30] and between pristinamycin and virginiamycin [50]. On the other hand, absence of cross-reactions between tetrazepam and other benzodiazepines, particularly diazepam, was confirmed by patch testing and oral provocation [89, 127].

Cross-reactions in fixed drug eruptions were also found among different sulfonamides, among the three piperazine derivatives (hydroxyzine, cetirizine, and levocetirizine) [128], and oxicams (tenoxicam and piroxicam) [66, 70]. This pattern of cross-reactivity between piroxicam and tenoxicam, observed in all cases of fixed drug eruptions studied, does not occur in other patterns of CADR from oxicams. In patients with photosensitivity from piroxicam, tenoxicam is safe, as shown by photopatch testing and drug challenge [40, 66].

Another particular pattern of cross reaction was shown in photopatch tests between the arylpropionic NSAIDs, ketoprofen, suprofen, and tiaprofenic acid in photoallergic contact dermatitis, and the lipid lowering agent, fenofibrate, in systemic photosensitivity [111, 129].

Unfortunately, there is not always correlation between cross-reactivity in patch testing and oral provocation, as in patients who react only to carbamazepine in the patch test, but do not tolerate other aromatic antiepileptics [65].

Core Message

› Patch tests with drugs are specific and can be important to study relevant cross-reactions between drugs.

26.4 Conclusions: Interpretation of Patch Test Results

Patch tests results in the study of drug eruptions should be interpreted very carefully.

A positive test, using nonstandardized products, has to be checked in controls to exclude false positive reactions. A true positive test can be regarded as a sign of immunological reactivity of the patient and should be taken seriously, if compatible with the history. Readministration of the drug should be avoided as it can again elicit an adverse reaction, usually, a more severe one.

A negative test result does not exclude hypersensitivity or an adverse drug reaction. The test method might not be adequate due to another pathomechanism, the bioavailability of the test material might have been insufficient, the wrong drug may have been tested (history and drug records can be surprisingly inaccurate), or the right drug may have been tested but the allergen could be a metabolite. Thus, a negative test result does not allow a definitive conclusion.

If necessary, other tests have to be performed, such as prick, scratch and intradermal skin tests or a challenge (provocation) test [48]. In vitro tests for IgE (RAST) exist for some drugs, as well as lymphocyte stimulation/transformation tests. However, these tests are rarely available or performed on a routine basis and their sensitivity and specificity has yet to be precisely evaluated.

In conclusion, although many suspected patients have negative reactions, it remains worthwhile to perform patch tests in patients with delayed CADRs. They can confirm a clinical imputability and avoid an eventual drug reintroduction with more severe consequences. In very particular cases, they can also give important information on cross-reacting drugs.

Core Message

› It is worthwhile to perform patch tests in individual patients with a suspected drug eruption.

26.5 Classic Articles and Monographs

Barbaud A, Gonçalo M, Bruynzeel D, Bircher A (2001) Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Derm 45:321–328.

In detail is described how to perform skin tests in CADRs. The presented guidelines are proposed by the Working party of the European Society of Contact Dermatitis for the study of skin testing in investigating CADRs.

Kauppinen K, Alanko K, Hannuksela M, Maibach H (eds) (1998) Skin reactions to drugs. CRC, Bocca Raton

This book gives extensive information on cutaneous adverse reactions and challenge tests, how to perform skin tests and in whom.

Pichler WJ (ed) (2007) Drug hypersensitivity. Karger AG, Basel

This book gives an extensive overview on the pathomechanisms of especially type 4 allergy involvement in adverse drug reactions.

26

[AU5] ## References

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Chapter No.: 26

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