Chapter 24

# Patch Testing in Adverse Drug Reactions

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Contents



**Core Message**

- A drug eruption is an adverse skin reaction caused by a drug used in normal doses and presents a wide variety of cutaneous reactions.

## 24.1 Introduction

A drug eruption is an adverse skin reaction caused by a drug used in normal doses. Systemic exposure to drugs can lead to a wide variety of cutaneous reactions, ranging from erythema, maculopapular eruptions (the most frequent reaction pattern), acrovesicular dermatitis, localized fixed drug eruptions, to toxic epidermal necrolysis and from urticaria to anaphylaxis (Figs. 1, 2). The incidence of these eruptions is not exactly known; 2%–5% of inpatients experience such a reaction and it is a frequent cause of consultation in dermatology [1–3]. Topically applied drugs may cause contact dermatitis reactions. Topical sensitization and subsequent systemic exposure may induce dermatological patterns similar to drug eruptions or patterns more typical of a systemic contact dermatitis, like the "baboon syndrome" (Chap. 16). It is clear that, in these situations, patch testing can be of great help as a diagnostic tool [4].

In patients with drug eruptions without previous contact sensitization, patch testing seems less logical, but is still a strong possibility, as systemic exposure of drugs may also lead to T-cell sensitization and to delayed type IV hypersensitivity reactions [5–8]. The value of patch testing in adverse drug reactions has not always been appreciated, but there is growing interest in this field. Positive test results can be very helpful, mainly as a complementary tool in drug imputation, but also for studying cross-reactions and understanding pathomechanisms involved in drug eruptions [9].

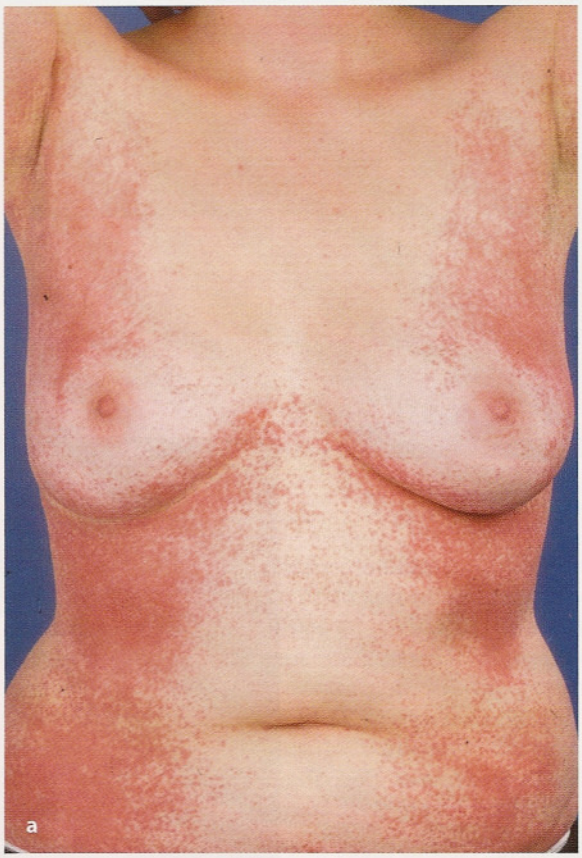


**Fig. 1a–c.** Acute generalized exanthematous pustular eruption (AGEP) due to phenobarbital (**a**). The detail shows numerous vesicles (**b**). The patch test with phenobarbital was clearly positive with vesicles and few pustules on day 2 (**c**)

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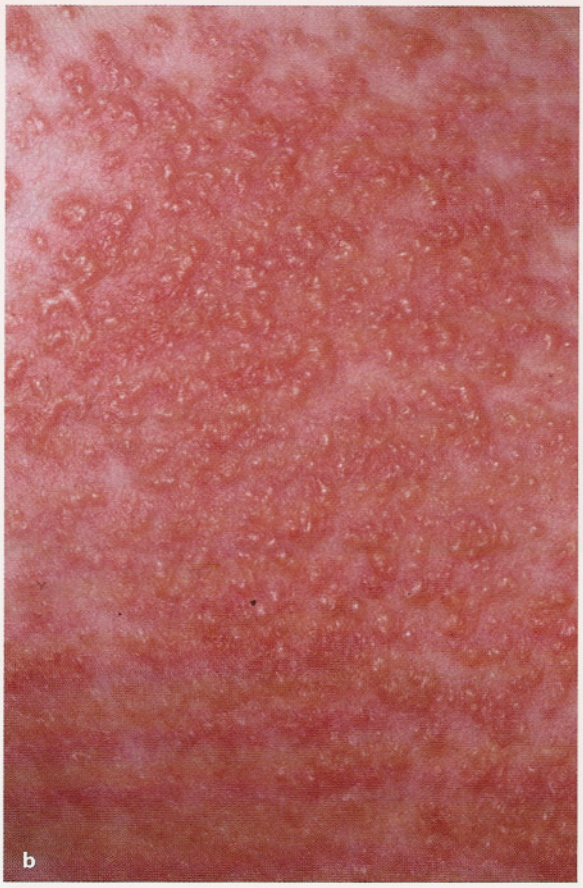

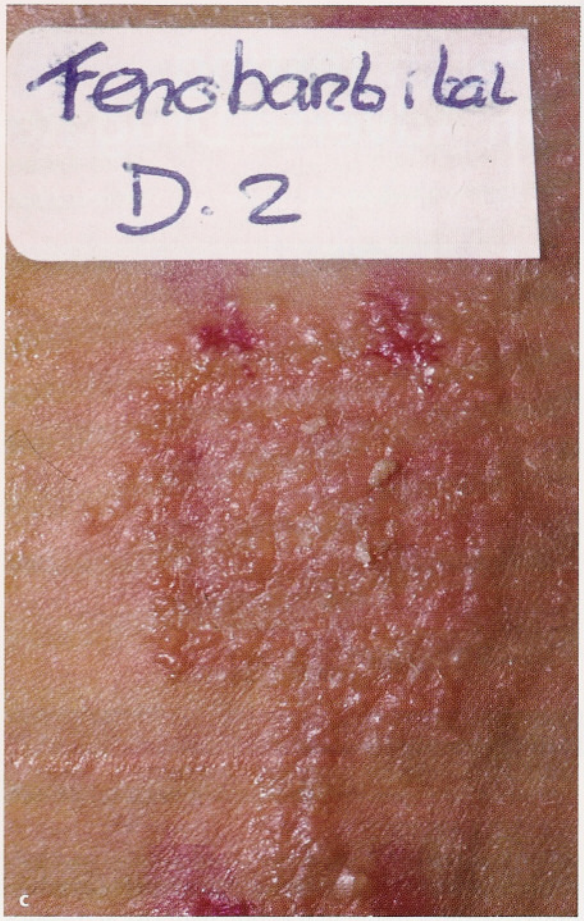


Fig. 1b, c.

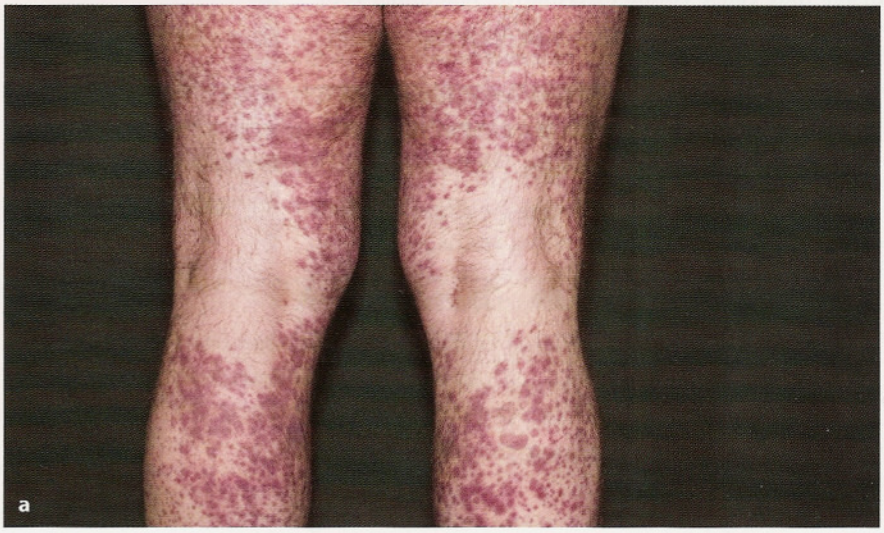

Fig. 2a–c.
Erythema multiforme-like drug eruption due to tetrazepam (a). Close up shows target lesions (b). Patch test with tetrazepam was positive both at 1% and 10% (c) (courtesy of PJ Frosch [89])

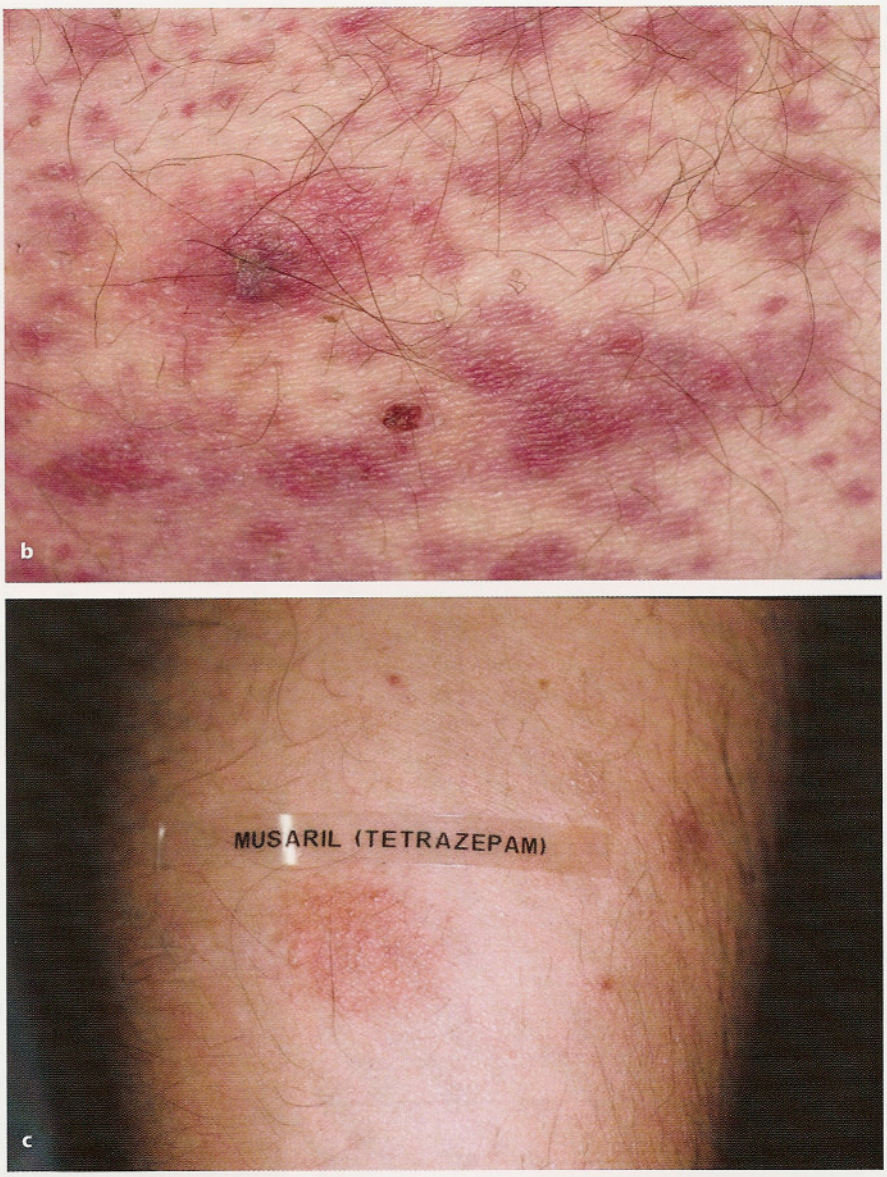


Fig. 2b, c.
Erythema multiforme-like drug eruption due to tetrazepam (a). Close up shows target lesions (b). Patch test with tetrazepam was positive both at 1% and 10% (c) (courtesy of PJ Frosch [89])

## 24.2 Pathomechanisms

Most adverse drug reactions are probably not allergic at all, but are caused by pharmacological properties of the drug, special sensitivity of the patient, or events such as accumulation and interactions. Usually it is not possible to decide from the clinical picture which mechanism is involved. The pseudo-allergic (anaphylactoid) reaction, observed with acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs, is an example of a nonimmunological reaction mimicking a true (type I) allergic reaction due to nonspecific release of large amounts of histamine and other mediators of inflammation [10]. Allergic drug reactions can be classified according to the immunological reaction types of Gell and Coombs (Chap. 2), but often, it is not one isolated immunological mechanism that is responsible for the event: combinations of type I and IV reactivity exist [11]. Delayed type IV hypersensitivity involving drug (or drug metabolite) specific T-cells have been documented in several patterns of drug eruptions. In maculopapular exanthema, specific T-cells were isolated from the skin and blood during the acute episode and, later, from positive patch tests [12]. Specific T-cells have been documented in other patterns of drug eruptions, where the different clinical aspects of the

eruption depend on the preferential activity of the T-cell: IL-5 production with eosinophil recruitment and activation in the drug hypersensitivity syndrome (DHS) or drug reaction eosinophilia and systemic symptoms (DRESS), production of the chemokine CXCL8 (IL-8) with preferential neutrophil recruitment in acute generalized exanthematic pustulosis (AGEP) or a T-cell cytotoxic activity in exanthems, bullous lesions, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis [6, 12–16]. 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, which induces lesional reactivation shortly after drug exposure, both after drug intake or topical application as a patch or open test [13, 17]. Delayed type hypersensitivity is also involved in some photosensitive drug reactions, mainly in those with an eczematous pattern [18, 19].

Therefore, this makes patch testing suitable in several drug eruptions other than dermatitis. Nevertheless, sometimes it is not the drug itself but a systemic metabolite that is the hapten responsible for the adverse reaction. This may be a cause of false-negative test results if the test is performed with the drug itself and not with the metabolite, which is usually not known or not available. Although skin metabolism is quite efficient, some drugs are not metabolized by skin cells [7].

**Core Message**

- A wide variety of clinically different adverse eruptions may be T-cell-mediated.

## 24.3 Patch Test Indications

The diagnosis of a drug eruption and the imputation of the culprit drug are performed mainly on clinical grounds, based on chronological and semiological criteria: the clinico-evolutive pattern of the eruption, its chronological relation with the initiation and suspension of the drug, and data on a previous drug reaction (accidental rechallenge) [20]. No single test can replace a good characterization of these parameters. Even in cases where very accurate data is available, which, most often, is not the case, and especially if the patient is on multiple drugs, the imputability index for a single drug is very low. Drug reintroduction would be the more definitive test for confirming the culprit drug, but it does not always reproduce the skin reaction and it is often contraindicated due to the risk of inducing a severe drug reaction, as in toxic epidermal necrolysis or in the hypersensitivity syndrome. Therefore, complementary clinical and laboratory investigations can then be performed in order to try to confirm, and seldom to exclude, an imputable drug.

Patch testing with drugs is simple to perform and is a relatively safe method of investigation. The risk of reactivation of the drug eruption is very low. Serious immediate reactions evoked by patch testing are rare [21–25], the risk is considerably lower compared with intracutaneous (i.c.) tests. Thus, the patch test is a good test to start with. If patch tests are negative, prick or scratch, i.c. tests, and a provocation test, performed sequentially in a hospital setting, may be the next steps [9].

Patch testing in the study of drug eruptions has been performed for many years, but not as a systematic investigation. Therefore, controlled studies with large numbers of patients with well characterized patterns of drug eruptions induced by different drugs are still lacking. Nevertheless, there are many reports showing that positive patch tests are found relatively often in cases of eczematous eruptions, maculopapular and delayed urticarial rashes, and AGEP (Table 1). Nevertheless, the frequency of positive tests ranges from 7.5% to 43%, depending on the selection of patients, the pattern of drug eruption, and the drugs involved [26, 27]. Positive patch tests with carbamazepine, tetrazepam, synergistins, and aminopenicillins are observed in more than 50% of the cases with delayed reactions [9, 28–37]. Fixed drug erup-

**Table 1.** Patch test results in patients with a possible adverse drug eruption, classified according to the type of eruption (adapted from [26] and [27])

| Eruption | Number of positives/patients (%) | | | |
|---|---|---|---|---|
| | Osawa et al. [26] ($n$=197) | | Barbaud et al. [27] ($n$=72) | |
| Maculopapular | 10/72 | (14) | 16/27 | (59) |
| Erythroderma | 8/15 | (53) | 5/7 | (71) |
| Eczematous | 9/17 | (53) | 3/9 | (33) |
| Erythema multiforme (EM) | 6/29 | (21) | | |
| Lichenoid | 2/11 | (18) | | |
| Photosensitivity | | | 4/4[a] | (100) |
| Fixed eruptions | 2/6 | (33) | 0/3 | |
| Urticaria/angioedema | | | 2/18 | (11) |
| Miscellaneous | 15/47 | (32) | 1/6[b] | (17) |
| Total | 62/197 | (31) | 31/72 | (43) |

[a] Photopatch test. [b] Positive test in AGEP

tions are unique, T-cell-mediated eruptions, so we can expect to find positive tests on the residual lesions in a high percentage of cases [12, 17]. Alanko [38] found as many as 26 out of 30 cases (87%) [17, 39]. In photosensitive eruptions, when it is not a clearly phototoxic reaction, photopatch tests can be rewarding [18, 40]. Examples of drugs reported to give positive patch test reactions are shown in Tables 2–5.

## Core Message

- Positive patch tests are found especially in eczematous and maculopapular eruptions, fixed eruptions, and, sometimes, in urticarial and photosensitive eruptions.

**Table 2.** Examples of drugs reported to elicit positive photopatch test reactions in patients with photosensitive adverse drug eruptions. The test concentrations and vehicles are those mentioned by the authors. The UVA test dose was usually 5 J/cm² but ranged from 4.5 J/cm² to 15.5 J/cm². (*acet.* Acetone, *aq.* water, *pet.* petrolatum)

| Drug | Test concentration, vehicle | Reference |
|---|---|---|
| Actarit[a] | 1% pet. | [56, 57] |
| Althiazide[b] | 10% pet./aq. | [58] |
| Amitriptyline[a] | 5% pet. | [59] |
| Carbamazepine | 0.01% pet. | [60] |
| Clomipramine[a] | 0.1% pet. | [61] |
| Chloroquine sulfate | – | [62] |
| Chlorpromazine[a] | 1% aq., pet. | [57] |
| Doxycycline[a] | 10% pet. | [63] |
| Flutamide[a] | 1–20% acet., pet. | [64, 65] |
| Griseofulvin | 1% pet. | [66] |
| Hydrochlorothiazide[a] | 1–10% pet. | [67] |
| Lomefloxacin[a] | 1–10% pet. | [40, 67, 68] |
| NSAIDs[a] | 1–10% pet. | [18, 69] |
| Ampiroxicam[a] | 1% pet. | [70] |
| Ketoprofen[a] | 1% pet. | [47, 176] |
| Piroxicam[a] | 1% pet. | [18, 19, 71–74] |
| Tiaprofenic acid | 1% pet. | [47] |
| Promethazine[a] | 0.1–1% pet. | [57] |
| Pyridoxine HCl | – | [75] |
| Pyritinol | 20% pet. | [76] |
| Quinidine | 0.1% aq. | [77] |
| Quinine | 0.1% aq. | [77] |
| 4-Quinolines[a] | 10% pet. | [78] |
| Simvastatin[a] | 10% pet. | [79, 80] |
| Tetrazepam[a] | 10% pet. | [81] |
| Thioridazine | 1% pet. | [57] |
| Triflusal[a] (HTB[c]) | 1% pet. | [82] |

[a] Tests in controls reported.
[b] Positive tests with UVB, not with UVA.
[c] *HTB* 2-hydroxy-4-trifluoro-methyl benzoic acid, a triflusal metabolite

**Table 3.** Examples of drugs reported to elicit positive patch test reactions in patients with adverse drug eruptions. The test concentrations and vehicles are those mentioned by the authors. (*alc.* Alcohol, *aq.* water, *eth.* ethanol, *pet.* petrolatum)

| Drug | Test concentration, vehicle | Reference |
|---|---|---|
| Aminoglycosides | 20% pet. | [26] |
| Anesthetics, local | 0.5–2% aq. | [83] |
| Atenolol[a] | 10% pet. | [84] |
| β-Lactam antibiotics[a] | 1–20%, pet. | [11, 28, 41, 45, 85–87] |
| Benzodiazepines[a] | 1% aq., 5–10% pet. | [30–33, 88, 89] |
| Bucillamine[a] | 1% pet. | [90] |
| Carbamazepine[a] | 0.1–10% pet. | [26, 34–36, 60] |
| Carbenicillin | 5% aq. | [91] |
| Captopril[a] | 0.1–3% pet. | [26, 92] |
| Celecoxib[a] | 10% pet | [93] |
| Cephalosporins | 5–20% aq., pet. | [11, 26, 41, 94–96] |
| Cimetidine[a] | 1% aq. | [97] |
| Clindamycin phosphate | 1–20% pet., aq. | [98, 99] |
| Codeine phosphate | 0.05% aq. | [100] |
| Dihydroquinidine[a] | pulverized tablet | [101] |
| Diltiazem[a] | 1% pet., saline | [102, 103] |
| Ephedrine HCl[a] | 5% aq. | [104] |
| Erythromycin base[a] | as is –2.5% pet. | [101, 105] |
| Gold sodium thiomalate | 5% pet. | [26] |
| Heparins | as is | [106– 109] |
| Hydromorphone[a] | 2% aq. | [110] |
| Metoprolol[a] | 10% pet. | [84] |
| Nifuroxazide[a] | 10% pet.; 1–0.001% aq. | [111, 112] |
| Nystatin | 30,000 IU/g PEG | [113] |
| Oxprenolol | 10% pet. | [84] |
| Oxyphenbutazone[a] | 1–5% pet. | [114, 115] |
| Penicillin G[a] | 100,000 units/ml aq. | [11, 42, 85, 91, 116] |
| Penicillins[a] | 1–20% pet. | [26, 28, 45] |
| Phenazone[a] | 5% pet. | [117] |
| Phenobarbital | 1–20% pet. | [26] |
| Phenylbutazone | 1–5% pet. | [114, 115, 118] |
| Phytotherapeutics: *Herba solidaginis* extr. | as is; 1:10 | [119] |
| Piroxicam[a] | 1–10% pet. | [26] |
| Piperazine | 1% aq. | [114] |
| Pravastatin | pulverized tablet | [120] |
| Pristinamycin | 1–10% aq., pet. | [29] |
| Propranolol[a] | 10% pet. | [84] |
| Propicillin | 20% pet. | [121] |
| Pyrazinamide | 1–10% alc. | [122] |
| Ranitidine[a] | 1% pet. | [123] |
| Sertraline[a] | 5–10% pet., eth. | [124] |
| Sodium valproate | 1–5% pet. | [26] |
| Spiramycin[a] | 5% pet. | [102] |
| Stepronin[a] | 18% sol. | [125] |
| Sulfamethoxazole[a] | as is | [43] |
| Sulfonamide[a] | 10% pet. | [102] |
| Tiopronin | 0.3–5% pet. | [26, 126] |
| Tobramycin | 5% aq. | [98] |
| Virginiamycin[a] | 0.5% pet. | [102] |
| Vitamin K[a] | 0.1% pet. | [127] |
| Zinc acexamate[a] | 5% aq. | [128] |

[a] Tests in controls reported

Table 4. Examples of drugs reported to elicit positive epicutaneous tests in fixed-drug eruptions, using an open or occlusive technique. The test concentrations and vehicles are those mentioned by the authors. (*alc.* Alcohol, *aq.* water, *DMSO* dimethylsulfoxide, *pet.* petrolatum)

| Drug | Test concentration, vehicle | Reference |
|---|---|---|
| Acyclovir | 5% pet. | [129] |
| Aminophylline | 10% pet. | [130] |
| Amlexanox | 50% pet. | [131] |
| Apronal | 5% pet. | [130] |
| Barbiturates | 10% pet., alc. | [38, 130] |
| Carbamazepine | 10% pet., alc. | [38] |
| Chlormezanone | 10% pet., alc. | [38, 130] |
| Citiolone | 10% DMSO | [132] |
| Ciprofloxacin | 10% pet. | [133] |
| Clarithromycin | 10% aq. | [134] |
| Dipyrone | 10% pet. | [130] |
| Doxycycline | 10% pet., alc. | [38, 130] |
| Ethenzamide | 20% pet. | [135] |
| Ibuprofen | 10% pet. | [130] |
| Mefenamic acid | 10% pet. | [130] |
| Metronidazole | 50% pet | [136] |
| Nimesulide | 1–10% pet. | [17, 137] |
| Ofloxacin | 20% pet. | [138] |
| Phenazone derivatives | 10% pet., alc. | [38, 130] |
| Piroxicam | 1–10% pet. | [17, 139] |
| Promethazine | 10% pet. | [130] |
| Sulfasalazine | 10% pet. | [140] |
| Sulfonamides | 10% pet., alc. | [38] |
| Trimethoprim | 10% pet., alc. | [38, 39] |
| Tenoxicam | 1–10% pet | [17] |

Table 5. Examples of drugs and chemically related materials which may, after contact sensitization, elicit systemic contact dermatitis when used systemically [4, 175]

| Drug | Reference |
|---|---|
| Amantadine | [141] |
| Aminophylline | [142] |
| Clonidine | [143] |
| Corticosteroids | [144–148] |
| Erythromycin | [105] |
| Estradiol | [46] |
| Ethylenediamine | [142, 149] |
| Ephedrine HCl | [104] |
| 5-Fluorouracil | [150] |
| Gentamycin | [151] |
| Gold salts | [152, 153] |
| Heparins | [154] |
| Hydroxyquinolines | [155, 156] |
| Hydroxyzine | [149, 157] |
| Imidazoles | [46, 158, 159] |
| Lignocaine, local anesthetics | [83, 160–162] |
| Mitomycin C | [163–165] |
| Neomycin | [156] |
| Netilmycin | [151] |
| NSAIDs: | |
| Arylpropionic acid derivatives | [47] |
| Arylalcanoic acid derivatives | [166, 167] |
| Pyrazolone derivatives | [168, 169] |
| Nystatin | [170] |
| Pantothenic acid (vitamin B5) | [171] |
| Penicillins | [4] |
| Sorbic acid | [172] |
| Sulfonamides | [4] |
| Synergistins | [173] |
| Tetraethylthiuram disulfide | [4] |
| Thimerosal | [174] |

## 24.4 Technique and Test Materials

It can take weeks before skin reactivity is measurable by patch testing. Thus, it is advisable to wait several weeks after the rash has gone to perform the patch tests. How long exactly is not known, but 6 weeks is usually advised [9, 41, 42].

Patch testing is performed in the generally accepted way on the back, as in contact dermatitis [9]. In particular cases, such as in fixed eruptions, reactivity occurs only in skin areas where the skin reaction has occurred [43, 44]. The application time is usually 2 days, but, occasionally, it can be convenient to remove tests at D1 [45]. Readings are performed at D2 and at D3 or D4, according to the International Contact Dermatitis Research Group (ICDRG) guidelines.

In fixed eruptions, the test materials are applied on an inactive, residual lesion, usually for one day, with occlusion as in patch testing. The residual pigmentation is a useful marker to indicate the area to apply the tests. Readings are performed at D1 and D2 or at D3, if previously negative [17]. Another test is applied on normal skin on the back and serves as a negative control. Alanko [38] prefers an open test, as, sometimes, positive reactions are seen only in the first 24 h, which makes observations necessary during the first 24-h period. A reaction is regarded as positive when clear erythema is visible for at least 6 h, but often, we can observe an eczematous or bullous reaction, sometimes mimicking the fixed drug eruption [17].

In drug photosensitivity, photoepicutaneous patch tests can be performed as in photoallergic contact dermatitis, using mainly UVA irradiation, at a dose of 5 J/cm$^2$ [18].

There is not much knowledge available about the ideal test concentrations of drugs. Concentrations

found in textbooks are often based on experiences with contact dermatitis patients. Sometimes, these concentrations seem to be too low in cases of drug eruptions. Recommended concentrations are usually between 1% and 20% of the pure chemical, but we need to know the safe ranges of test concentrations, for which, larger studies with patients and controls are needed. For example, carbamazepine, hydrochlorothiazide, propranolol, sulfamethoxazole, and trimethoprim did not evoke reactions when tested at 20% in petrolatum in 200 volunteers [1]. In patients with delayed exanthematous eruptions due to carbamazepine, ampicillin, and amoxicillin patch-test concentrations of 1% and 5% are sufficient, as all patients reacting at 20% also reacted at 1% or 5% pet [28, 45]. In cases of very severe drug eruptions, it is advisable to start with lower concentrations to prevent reactivation of the eruption [9].

If the pure drug is not available, which is often the case, the test can be done with the drug as such, in powdered form or in solutions for oral, i.v., or i.m. use. The amount of active drug in a tablet varies, but is approximately 20% (w/w). Serial dilutions can be helpful. Petrolatum and water are the most frequently used vehicles, but ethanol and dimethylsulfoxide (DMSO) can be more adequate for certain drugs [46]. A pharmacist can give advice on a suitable vehicle for maximum penetration and bioavailability.

Whenever possible, chemically related compounds or other drugs of the same pharmacological group are tested in order to obtain information on possible cross-reactivity. Sometimes, the pattern of cross-reactivity may be very informative for the patient and the doctor. In this way, cross-reactivity was demonstrated between: amoxicillin and ampicillin [28]; in more than half of the cases between pristinamycin and virginiamycin [29]; in systemic photosensitivity for the arylpropionic nonsteroidal anti-inflammatory drugs (NSAIDs), ketoprofen and tiaprofenic acid, and the hypolipemiant agent fenofibrate [47]. There is cross-reactivity between piroxicam and tenoxicam in fixed drug eruptions, whereas tenoxicam is safe in piroxicam photosensitive patients, as shown by photopatch testing and drug challenge [17, 19].

When tests are 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 [48–51]. Occasionally, they are the cause of false positive reactions (irritation, low pH), and induce nonrelevant positive patch test reactions in previously contact-sensitized patients [51]. Testing with pure drugs or with low concentrations of the commercial products seldom gives false positive reactions. Nevertheless, a positive reaction with a non-standardized drug concentration needs to be checked in at least 20 controls.

Although rarely encountered, anaphylactic reactions can occur due to topical application of drugs, e.g., penicillins, neomycin, or bacitracin [21–23]. For safety reasons, it is practical to observe the patient for approximately half an hour after application of the test material. Another adverse patch test effect is sensitization by patch testing; this is rarely seen, even with penicillins [52].

False-negative reactions can be expected, either because the responsible hapten is a drug metabolite that is not formed in the skin, because the vehicle or the concentration is not adequate, or because, as occurs in viral infections, the drug eruption is due to other concomitant factors that may enhance individual hypersensitivity [37, 53].

**Core Message**

- Patch tests are best performed not earlier than 6 weeks after disappearance of the rash.

## 24.5 Relevance and Consequences

The tests should be interpreted very carefully. A positive test has to be checked with the controls to exclude false-positive reactions. Although ethical problems may arise over the use of controls, we can perform control tests on individuals who take the drug but who developed a drug eruption from a different drug. 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, which might be even more severe.

A negative test result far from excludes 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, the right drug may have been tested but the allergen could be a metabolite, and so on. 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 tests or even a challenge (provocation) test [54]. The provocation test is regarded as the gold standard, but occasionally also gives false negatives [55]. In vitro tests for IgE (RAST) exist for some drugs, as well as lymphocyte proliferation/activation tests. However, these tests are rarely available and not performed on a routine basis.

In conclusion, although many suspected patients have negative patch test reactions, it remains worthwhile to perform the tests on individual patients.

They can confirm a clinical imputability and avoid any eventual drug reintroduction with more severe consequences and, in very particular cases, can give important information on other cross-reacting drugs.

## Core Message

- It is worthwhile to perform patch tests on individual patients with a suspected drug eruption.

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