

Usefulness of skin testing in cutaneous drug eruptions in routine practice

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Background: Cutaneous drug eruptions are common side-effects. The imputation score combining intrinsic (chronology, clinical and paraclinical signs) and extrinsic criteria used in Pharmacovigilance Centres is insufficient alone to identify with certainty a responsible drug.

Objective: To evaluate the imputation score before and after performing skin testing in patients with cutaneous drug eruptions.

Patients/Methods: A single-centre retrospective study was performed on 339 patients tested between 2001–2006. Imputation scores were calculated before and after skin tests for each cutaneous drug eruption according to the clinical type of skin eruption and the type of drug.

Results: Among 121 patients meeting inclusion criteria, 46% showed an increase of the imputation score as shown by 25/41 cases of maculo-papular exanthema, 4/11 cases of acute generalized exanthematous pustulosis and 17/41 cases of urticaria/anaphylaxis. The imputation score increased in 25/70 cases of the tested antibiotic drugs, in 14/56 cases of cardiovascular drugs, and it increased in 19 patients (34%) with I1 or I2 imputation scores before skin testing and in 29 (52%) with an I3 imputation score before skin testing.

Conclusions: Drug skin testing appeared useful in investigating cutaneous drug eruptions in routine practice, including not only drugs with a high imputation score (I3) but also those with a lower score (I1, I2). Drug skin testing should lead to oral rechallenge of drugs with negative tests in order to determine which drugs may be used safely.

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According to a French Health Products Safety Agency survey, 2% of hospitalized patients experience a cutaneous drug eruption (1). Algorithms used by pharmacovigilance centres (2) to calculate an intrinsic imputation score (Table 1) are frequently insufficient to identify the responsible drug causing a cutaneous eruption. This score combines intrinsic (chronology, clinical and paraclinical signs) and extrinsic criteria. Drug skin testing aims to improve the management of a cutaneous drug eruption. Its diagnostic value is well known in beta-lactam type I hypersensitivity reaction, but studies of its value in other types of hypersensitivity reaction

are sparse (3). The aim of our study was to determine the usefulness of drug skin testing in routine practice, in terms of raising the intrinsic imputation scores for different types of cutaneous drug eruptions and for different classes of drug.

Patients and Methods

Patients

The study was retrospectively conducted in a single department of dermatology of a French University Hospital (Reims). All patients attending for drug skin testing for a cutaneous drug eruption between

Table 1. Criteria for intrinsic imputation score ([2])

Chronological criteria (C)							
Drug administration: time to occurrence of event	Highly suggestive			Compatible		Incompatible	
Drug rechallenge	R+	R0	R–	R+	R0	R–	
Evolution after drug withdrawal:							
Suggestive	C3	C3	C3	C3	C2	C1	C0
Inconclusive	C3	C2	C3	C3	C1	C1	C0
Non-suggestive	C1	C1	C1	C1	C1	C1	C0

Clinical/laboratory score (S)

Clinical or laboratory aspects	Suggestive of drug cause			Other possibilities		
Reliable specific laboratory test (L)	L+	L0	L–	L+	L0	L–
Other explanation not attributable to drug:						
Absent (after appropriate work-up)	S3	S3	S1	S3	S2	S1
Possible (present or not sought)	S3	S2	S1	S3	S1	S1

L0: test not available.

Intrinsic imputability score (I)

Semiological criteria	S1 doubtful	S2 plausible	S3 probable
Chronological criteria			
C0 excluded	I0	I0	I0
C1 doubtful	I1	I1	I2
C2 plausible	I1	I2	I3
C3 probable	I3	I3	I4

I0: unlikely, I1: doubtful, I2: possible, I3: probable, I4: very probable.

September 2001 and January 2006 were included. Inclusion criteria were:

- Patients with a recent cutaneous drug eruption diagnosed and classified by a dermatologist as urticaria/anaphylaxis, maculo-papular exanthema, acute generalized exanthematous pustulosis, eczematous eruption, fixed drug eruption, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) or other types (erythema multiforme, vasculitis, lichenoid eruption);
- A well-established chronology between drug intake and skin rash;
- Skin testing performed between 6 weeks and 6 months after recovery of a cutaneous drug eruption without any recent treatment with (local or general) corticosteroids or antihistamines.

Exclusion criteria were:

- Potentially lethal cutaneous drug eruptions such as Stevens-Johnson syndrome and Lyell's syndrome;
- Cutaneous drug eruption secondary to vaccination or local anaesthetic injection.

Methods

For each patient, data were retrospectively recorded from their files. They included (i) demographic data

(sex, age at diagnosis), (ii) medical history (including previous episodes of cutaneous drug eruption and immuno-suppression), (iii) characteristics of the recent cutaneous drug eruption episode (dates of onset and recovery, type of skin rash, hospitalization) and (iv) type of the potential culprit drug(s) (anaesthetic, antibiotic, non-steroidal anti-inflammatory drug, cardiovascular drug, analgesics, other).

An intrinsic imputation score (from I0 to I4: I0 unlikely, I1 doubtful, I2 possible, I3 probable, I4 very probable) before skin tests was calculated according to Moore et al. (2) for each potential culprit drug (Table 1). This score is established from chronological and clinical data. The chronological score (C0 to C3) takes into account the delay between drug intake and the onset of the skin rash, an eventual rechallenge of the drug, and evolution after drug withdrawal. The delay between the first drug intake and the onset of the skin rash is considered as:

- *Very suggestive* between 7 and 21D for a maculo-papular exanthema, eczema, erythema multiforme, vasculitis, lichenoid eruption, between a few hours and 48 hours for acute generalized exanthematous pustulosis and fixed drug eruption, between a few minutes and a few

hours for urticaria/anaphylaxis, and between 20 and 40D for DRESS;

- *Suggestive* if delay was less than those mentioned above;
- *Incompatible* if the drug was taken after the onset of the skin rash.

The clinical score (S1 to S3) is based on the clinical and paraclinical aspects of the eruption, the results of specific investigations and the possibility of a non-drug-induced explanation (Table 1). Since always considered as aspecific, the skin rash was always classified in the column 'other possibilities'. An imputation score was then calculated after drug skin testing. When several drugs were tested, an imputation score was calculated for each drug. The maximum imputation score for each patient was then established, corresponding to the highest score among all tested drugs. Drug skin testing included prick-tests, patch-tests and intradermal tests according to standardized techniques established by the European Society of Contact Dermatitis workshop (4) including immediate (20 min) and late (2, 4 and 7D) readings.

Patch-tests were performed on patients' backs (or on the initially affected site for a fixed drug eruption) using the commercial form of the drug and, when available, the pure substance. Tablets and capsule contents were tested diluted at 30% in petrolatum and water. The results of patch testing were recorded according to the International Contact Dermatitis Research Group criteria (5).

Prick-tests were performed on the same day as patch-tests, on the forearm using the commercial form of the drug. Pure forms of the drug and excipients were also tested whenever possible. In cases of urticaria, the drug was tested at increasing dilutions of 10^{-3} , 10^{-2} , 10^{-1} and then pure. The test was considered positive when the papule diameter reached at least half of that of the positive control (codeine phosphate 9% or histamine 10 mg/ml).

Intradermal tests were performed only when prick-tests were negative. They were not performed in cases of erythema multiforme, vasculitis or DRESS. For these purposes, patients were hospitalized for a day with a glucose solution infusion, which was removed only after at least 2 hours with a negative test and 6 hours after a positive test, with regular monitoring of blood pressure and pulse. Intradermal tests were performed using a sterile solution of the suspected drug, diluted at 10^{-4} , 10^{-3} , 10^{-2} and 10^{-1} in phenolated saline (0.5% phenol in 0.9% saline). They were performed on the back of the arm or on the extensor aspect of the arm, at increasing dilutions every 30 min, with 0.02 ml of solution, producing a papule of 4–6 mm

in diameter. A negative control with phenolated saline was systematically included. The reading made at 30 min was considered as positive if a papule greater than twice the initial papule diameter was observed. If negative, subsequent intradermal tests with increasingly higher serial dilutions were performed.

Results

Patients

Between September 2001 and January 2006, 339 patients were tested in our department for a suspicion of cutaneous drug eruption among whom 218 could not be included in the study for the following reasons: 37 patients had an eruption which was not diagnosed by a dermatologist, 20 were tested 6 months or later after the recovery of the eruption, 16 had unclear chronology of drug intake and 145 did not fit the other inclusion criteria. Finally, 121 patients were included in the present study (51 men and 70 women; mean age 52.5 years; median age: 54 years, range: 3–89). A total of 45 patients (37.5%) had a previous history of cutaneous drug eruption, 40 (33%) were hospitalized for the eruption and 6 (5%) had immuno-suppression.

The different types of cutaneous drug eruption were urticaria/anaphylaxis in 41 cases (34%), maculo-papular exanthema in 41 (34%), acute generalized exanthematous pustulosis in 11 (9%), eczematous eruption in 8 (7%), fixed drug eruption in 4 (3%) and another type (DRESS, erythema multiforme, vasculitis, lichenoid eruption) in 16 (13%).

A total of 343 drugs were tested in the 121 patients included and 80 patients (66%) had more than one drug tested. The different types of drugs tested were: antimicrobial drugs in 70 cases (20%), general anaesthetics in 65 (19%), cardiovascular drugs in 56 (16%), analgesics in 28 (8%), non-steroidal anti-inflammatory drugs in 25 (7%) and other drugs in 99 (29%).

Drug skin testing

Maximum imputation score before and after drug skin testing. Before skin testing, the maximum imputation score for the suspected drug(s) was I1 or I2 in 56 patients (46%) and I3 in 65 (54%), whereas none of the patients had a drug scored I4. After skin testing, the maximum imputation score remained I1 or I2 in 35 cases (29%) and became I3 in 56 cases (46%) or I4 in 30 (25%) (Table 2). Particularly, in 19 patients (34%) maximum imputation score went up from I1 or I2 before tests to I3 or I4 after skin testing and in 29 (52%) maximum imputation score

Table 2. Maximal imputation score before and after drug skin testing

MIS	Before skin tests No of patients (%)	After skin tests No of patients (%)
I1	43 (35)	24 (20)
I2	13 (11)	11 (9)
I3	65 (54)	56 (46)
I4	0 (0)	30 (25)
Total	121	121

MIS: maximal imputation score

went up from I3 before tests to I4 after skin testing. Overall, 56 patients (46%) showed an increase of maximum imputation score for their suspected drug(s) after skin testing (Table 2), meaning that, in those patients, the tests were positive for the most 'imputable' drug.

Maximum imputation score before and after skin tests according to the type of cutaneous drug eruption. The increase of the maximum imputation score for the suspected drug(s) after drug skin testing according to the clinical type of cutaneous drug eruption is shown in Table 3. In all but two cases, the drug with the maximum imputation score before tests was the drug with the maximum imputation score after tests. In seven cases, the maximum imputation score increased for two drugs or more. A majority of patients with a maculopapular exanthema (61%), half of patients with an eczematous rash or a fixed drug eruption, 41% patients with immediate hypersensitivity and one-third of patients with acute generalized exanthematous pustulosis showed a maximum imputation score increase for the suspected drug(s) (Table 3). For immediate hypersensitivity reactions, the maximum imputation score for the suspected drug(s) before tests was I1 in 8 cases (19%), I2 in 2 cases (5%) and I3 in 31 cases (75%), and none of the patients had a drug scored I4 before skin tests. After skin testing, the maximum imputation score became I1 for 5 patients (12%), I2 for 2 patients (5%), I3 for 21 patients (51%) and I4 for 13 patients (32%).

Imputation score before and after skin tests according to the drug type. The increase of the imputation score after drug skin testing according to the

Table 4. Increase of the imputation score according to the type of the suspected drug

Type of drug	No. of patients (%) with increase of the imputation score
Antimicrobial drugs	25/70 (36)
Cardiovascular drugs	14/56 (25)
Anaesthetics	6/65 (9)
NSAIDs	3/25 (12)
Analgesics	3/28 (11)
Other drugs	19/99 (19)

NSAIDs: non-steroidal anti-inflammatory drugs.

type of the suspected drug is shown in Table 4. An increase of imputation score for the suspected drug(s) was mainly observed for antimicrobial drugs (36% of cases) and cardiovascular drugs (25% of cases) (Table 4). The increase of the imputation score according to both the type of the suspected drug and the main clinical types of cutaneous drug eruptions are detailed in Table 5. For other types of cutaneous drug eruption, an imputation score increase was observed in only 4 out of 16 cases (25%), mainly when cardiovascular drugs (i.e., spironolactone, fluindione, diltiazem) were suspected. An increase of imputation score was mainly observed for antimicrobial drugs in maculopapular exanthema (47% of cases) or acute generalized exanthematous pustulosis (43% of cases) and for cardiovascular drugs in maculopapular exanthema (38% of cases) (Table 5).

Oral rechallenge. A total of 13 oral rechallenges were performed in 12 patients (10%) who had negative drug skin testing: 9 oral rechallenges were negative, 2 positive (in both cases causing urticaria) and 2 were stopped after completion because of malaise.

Discussion

The present study performed in a single University dermatology department confirms the feasibility and the potential usefulness of drug skin testing in cutaneous drug eruptions in routine practice. Some previous studies evaluating the use of skin testing in cutaneous drug eruptions have been published with

Table 3. Increase of the maximal imputation score according to the type of cutaneous drug eruption

Type of cutaneous drug eruption	No. of patients (%) with increase of the MIS	No. of patients (%) with increase of the MIS from I1 or I2 to I3 or I4	No. of patients (%) with increase of the MIS from I3 to I4
Maculo-papular exanthema	25/41 (61)	13/25 (52)	12/25 (48)
Eczematous rash	4/8 (50)	1/4	0/4
Fixed drug eruption	2/4 (50)	1/2	1/2
Urticaria/anaphylaxis	17/41 (41)	4/17 (23.5)	12/17 (70.6)
Acute generalized exanthematous pustulosis	4/11 (36)	1/4	2/3
Other type	4/16 (25)	3/4	1/4

MIS: maximal imputation score.

Table 5. Increase of the imputation score according to both the type of the suspected drug and the main clinical types of cutaneous drug eruption

Type of skin rash	Type of drug	No. of patients (%) with imputation score increase	Suspected drug
Maculo-papular exanthem	Antimicrobial drugs	17/36 (47)	Beta-lactams, gentamicin, pristinamycin, clindamycin, spiramycin, metronidazole
	Cardiovascular drugs	8/21 (38)	Enoxaparin sodium, nadroparin calcium, dalteparin sodium, amiodarone, diltiazem, sotalol, fenofibrate, digoxin
	NSAIDs	1/8 (12)	Naproxen
	Analgesics	3/11 (27)	Paracetamol, morphine sulfate
	Other drugs	10/30 (33)	iodixanol, cimetidine, hydroxyzine, ranitidine, acetylcysteine, ibuprofen, diazepam, tetrazepam, calcitonin, hydroxychloroquine
	Anaesthetics	0/4 (0)	
Acute generalized exanthematous pustulosis	Antimicrobial drugs	3/7 (43)	Amoxicillin, pristinamycin
	Cardiovascular drugs	0/2 (0)	
	NSAIDs	0/2 (0)	
	Analgesics	0/3 (0)	
	Other drugs	2/16 (12)	Omeprazole, citalopram
	Antimicrobial drugs	2/2 (100)	Levofloxacin, pristinamycin
Eczematous rash	Cardiovascular drugs	1/13 (8)	Spirolactone-altizide
	NSAIDs	0/1 (0)	
	Analgesics	0/1 (0)	
	Other drugs	1/10 (10)	Repaglinide
	Antimicrobial drugs	0/2 (0)	
Fixed drug eruption	NSAIDs	0/1 (0)	
	Other drugs	2/3 (67)	Cyamemazine, carbamazepine
	Anaesthetics	6/61 (10)	Suxamethonium chloride, pancuronium bromide
Urticaria/anaphylaxis	Antimicrobial drugs	3/17 (18)	Spiramycin-metronidazole, vancomycin, sulfamethoxazole-trimethoprim
	Cardiovascular drugs	0/6 (0)	
	NSAIDs	2/10 (20)	Diclofenac
	Analgesics	0/10 (0)	
	Other drugs	4/23 (17)	Zolmitriptan, naratriptan, hydroxyzine, amitriptyline

NSAIDs: non-steroidal anti-inflammatory drugs.

various methodologies and results. In the prospective study of Barbaud et al. the inclusion criteria were the same as in our series, but only one drug was tested per patient and the drug imputation score before testing was always high (I3), resulting in an overall positivity of skin tests of 72% (3), which was, therefore, much higher than our present result of 46%. In the later series of Lammintausta et al. (6) and Wöhrle et al. (7), which included 947 and 291 patients, respectively, the inclusion criteria were less strict since all patients with a suspicion of cutaneous drug eruption, even not seen and diagnosed by a dermatologist, were included. The positivity of drug skin testing was 10.8% (patch-tests) and 1.1% (prick-tests) for Lammintausta et al. (6) and of 24.4% (prick- and patch-tests) for Wöhrle et al. (7). In our present series, inclusion criteria reflect the usual practice of aetiological investigations of cutaneous drug eruptions in a dermatology department:

patients were investigated 6 weeks to 6 months after a recent cutaneous drug eruption episode, referred by a dermatologist who had already diagnosed and classified the skin rash. Those patients had frequently several suspected drugs, with imputation scores before tests varying from I1 to I3. In this respect, our inclusion criteria and overall results were similar to those of the series of Choquet-Kastylevsky et al. (8) which studied only 39 patients, but also showed an imputation score increase in 46% of cases (8).

Our present results show that is useful to test not only maculo-papular exanthema, urticaria/anaphylaxis and acute generalized exanthematous pustulosis as previously shown (3, 6–8) but also eczematous skin and fixed drug eruption (Table 2) when combining prick-tests, patch-tests and intra-dermal tests, though our sample size is too limited to conclude for the two latter, uncommon types of

Table 6. Skin tests results according the type skin test and the type of cutaneous drug eruption

Type of cutaneous drug eruption/type of skin tests	Prick-tests	Patch-tests	Intradermal tests
Urticaria/ anaphylaxis	3/40 (7.5%)	1/21 (4.8%)	10/26 (38.5%)
Maculo-papular exanthema	5/41 (12.2%)	12/38 (31.6%)	9/18 (50%)
Acute generalized exanthematous pustulosis	3/11 (27.3%)	4/11 (36.4%)	0/2
Eczematous rash	2/8	2/7	0/0
Fixed drug eruption	0/3	2/4	0/0
Other type	0/14	2/17 (11.8%)	0/14

cutaneous drug eruption. The combination of the three types of tests (patch- and prick-tests, intradermal tests) has to be done whenever possible for each patient. For maculo-papular exanthema (acute generalized exanthematous pustulosis) and immediate hypersensitivity, intradermal tests with immediate and late readings seems to be more sensitive than prick- and patch-tests (Table 6). In the literature, similar results were found. Maculo-papular exanthema, acute generalized exanthematous pustulosis, eczematous eruption, fixed drug eruption were investigated using patch-tests (3, 9–15) and, to a lesser degree, prick-tests (3, 9), with encouraging results, but intradermal tests appeared even more sensitive and specific in exploring immediate and delayed hypersensitivity reactions (3, 9).

When considering the suspected culprit drugs, antibiotics and cardiovascular drugs represent the two main classes tested in our series. They are also the two groups with the higher percentage of positive tests with 36% for antimicrobial drugs and 25% for cardiovascular drugs (Tables 4 and 5). In the literature, a number of antimicrobials were associated with high rates of skin eruptions (5–7% for aminopenicillins, 3–4% for antibacterial sulfonamides) and drug skin tests were reported to be useful in this context (16). Immediate hypersensitivity reaction to beta-lactams is the most known and studied reaction (17, 18). In the study conducted by Ponvert et al. in children, drug skin tests (prick-tests and intradermal tests) were positive in 86% of patients with immunoglobulin E-dependant sensitizations to beta-lactams (18). In delayed hypersensitivity reactions to beta-lactam, patch-tests were positive in 10–38% of cases (14, 19) and in 36% of 96 patients when combining patch-tests and intradermal tests (20). Patch-tests were also reported to be useful in testing other antimicrobial drugs, including cotrimoxazole (21), pristinamycin (3, 15, 22), vancomycin (23), aciclovir and valaciclovir (24, 25), fluoroquinolones (3, 26), and terbinafine (3). When

a cutaneous drug eruption to a cardiovascular drug is suspected, it is often crucial to know precisely if it may be responsible or not, since those drugs are generally essential and sometimes very difficult to replace. Drug skin tests were also reported to be useful for testing cardiovascular drugs, including heparin derivatives (3, 27), enoxoparin (3), fluindione (28), diltiazem (3, 29) and captopril (3). Interestingly, in our series we also tested a variety of general anaesthetic drugs, which represented 19% of the tested drugs; this is due to the long-established multidisciplinary consultation, which includes anaesthetists, in our department. Most of the anaesthetic drugs were suspected in immediate hypersensitivity reactions (92%). The imputation score increased for 6/65 drugs tested (9%). We included suxamethonium and pancuronium that are often used during general anaesthesia as neuromuscular blockers inducing muscle relaxation and that may cause IgE dependent or non-immunological urticaria. It was consistent with the fact that <20% of immediate reactions are thought to be of immunological origin (30). In this respect, drug skin testing may be also helpful for the understanding of drug allergy. Drug specific T-cells have been described in skin biopsies of positive patch-tests when testing maculo-papular exanthema (31–33). These T-cells often expressed both CD4 and CD8 phenotypes, with a majority of CD4+ clones. A Th2 orientation was frequently observed in CD4+ clones while CD8+ clones were usually Th1 and often cytotoxic (32).

Finally, our present results illustrate that it is not only interesting to test suspected drugs with a high imputation score (I3) but also those with a lower score (I1 or I2), which represented almost half of the patients (56/121) included in our series. This also suggests the lack of sensitivity of the classical imputation score used in routine practice to define the culprit drug in a cutaneous drug eruption (2). However, we could not calculate the negative predictive value of drug skin testing because of the retrospective nature of our study and the absence of systematic oral rechallenge of the drugs whose tests were negative. This could be explained by the 'better safe than sorry' approach generally applied in routine practice, consisting of forbidding all suspected drugs. This approach has the advantage of avoiding the risk of re-inducing the cutaneous drug eruption in a more severe form if the drug is given orally again. Nevertheless, oral rechallenge was performed in some previous studies. Lammintausta et al. found a negative predictive value of 93% and 87% in two studies corresponding to 17/246 and 136/1001 positive oral rechallenge (6, 34). Ponvert et al. (18) found a negative predictive value of 94% (17/271 positive oral

rechallenges), Messaad et al. (35) a negative predictive value of 82.4% (241/1372 positive rechallenges) in immediate drug allergy and Wöhrle et al. (7) a negative predictive value of 86.5% (14/104 positive oral rechallenge). Overall, drug skin tests seem to have a good negative predictive value. A negative drug skin testing of drugs considered as useful or indispensable for a patient should lead to oral rechallenge in order to tell the patient which drug(s) may be used for future use.

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