

Drug re-challenges in cutaneous adverse drug reactions: information and effectiveness in the long-term management of patients

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Abstract

Background: In patients with cutaneous adverse drug reactions (CADR), drug skin tests and re-challenge under hospital surveillance (RCH) are helpful. The aim of this study was to determine if patients with negative drug RCH can tolerate subsequent treatments with the same drugs.

Patients and Methods: Patients with a negative RCH in the last 10 years answered a telephone questionnaire which was delivered by the same investigator in order to determine if subsequently the patients were able to tolerate the drug with which they had a negative RCH and also to study the reasons why the drugs were not taken again.

Results: Six hundred and thirty-seven RCH were analyzed (349 patients, mean age 47 years), 134 drugs were taken again (group A) and 359 were not (group B). In group A, 12 reactions occurred in 10 patients (9%). In group B, drugs were not taken again because 76% of the patients evaluated for an intolerance to antibiotics or radiocontrast media did not require a new course of these products or because their general practitioner (GP) did not want to prescribe these drugs.

Discussion: Ninety percent of the RCH (88.5% of the patients) with a CADR followed by investigations and a RCH have a good tolerance to subsequent treatment with the RC drug. The mechanisms involved in this intolerance despite negative RCH are discussed.

Conclusion: The provocation test procedure, considered as useful by 88% of the patients, has a good negative predictive value. Furthermore, these investigations need to be accompanied by clear information on the patient and his GP.

Drug hypersensitivity reactions may affect up to 7% of the general population (1). They have a significant impact on clinical practice, drug development, and public health. A negative drug skin test does not exclude responsibility of the drug in cutaneous adverse drug reactions (CADR). With many different drugs, the negative predictive value (NPV) of a drug skin test has been estimated at 89.6% (2). Drug re-challenge (RC), under hospital surveillance, is useful for both immediate and nonimmediate adverse reactions (2–4), but is also used to determine whether a drug with negative reactions on skin tests can or cannot be tolerated by a patient.

The objective of this study was to determine whether patients diagnosed as nonallergic by drug skin tests and oral

provocation test (OPT) or substitution test (ST) with a drug by RC carried out under hospital surveillance (RCH) can tolerate subsequent treatments with the same drug.

Patients and methods

Patients

Patients referred to our department for a CADR, which occurred between January 1999 and April 2009, who had negative skin tests then RCH, either OPT or ST, were included.

The inclusion criteria were (i) a suggestive history of drug hypersensitivity; (ii) negative patch tests, prick tests, and

intradermal tests (IDTs) for injectable drug forms; (iii) negative RCH (OPT and/or ST) under hospital surveillance for the studied drug.

Exclusion criteria were (ii) difficulties during the long-term follow-up because of concomitant oncologic problems.

Methods

Skin tests

Patch tests, prick tests, and IDTs were carried out according to previously published guidelines (5). For the IDT, the injected volume was that which led to an injection papule diameter of 4–6 mm, considered as positive when the diameter at 20 min was twice those of the injection papule. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) were also skin tested.

Re-challenges

Patients underwent a standardized evaluation in our clinic at least 6 weeks after clinical symptoms of the suspected CADR were resolved. They were denied beta blockers, antihistamines, and systemic corticosteroids for 7 days and 1 month, respectively, before the RCH. Re-challenge was carried out only when skin tests results were negative. As previously described (2), six increasing dosages were administered *vs* placebo under hospital surveillance for 5 h after the last dosage. Readministration of radiocontrast media (RCM) or low-molecular-weight heparins were done as previously published (2). Patients were informed to give us a phone call if any adverse event would occur in the next 2 weeks.

Re-challenge was considered negative if nothing occurred after the usual daily dose had been administered and the following 2 weeks. For patients who received more than one drug during the initial CADR, other RC were performed. An OPT was carried out if the drug causality assessment was weak or if the drug was essential for the patient; a ST was performed if the drug imputation was high. Moreover in drug reaction with eosinophilia and systemic symptoms (DRESS), if another drug demonstrated as responsible, if the drug causality assessment was very weak, RCs with essential drugs were carried out in giving one dosage every 10 days.

Patient files and specific questionnaire

For all included patients, the following information was collected from our files: sex, age, initial clinical features during the CADR, date of occurrence of the CADR, address, and telephone number, and for each investigated drug, the results of drug skin tests and modalities of the RCH (OPT or ST) were recorded.

We performed a telephone survey in patients who had negative RC (OPT and ST) between January 1999 and April 2009. All patients were questioned by the same investigator. We sent a questionnaire by post to patients if we did not have a telephone number.

The reasons why some patients did not receive a new course of medication after having a negative RCH were analyzed. When patients received a course of the studied medication,

their tolerance was analyzed. Furthermore, we tried to evaluate the patients' opinions concerning the usefulness of drug allergy investigations.

According to re-administration of the drug, patients were classified into two groups, group A (drugs which were taken after a negative RCH) and group B (drugs which were not taken after RC). We compared the characteristics of the two groups.

The statistical unit was 'one drug with a negative RCH under hospital surveillance'. In group A, the number of non-tolerated drug intakes and their reported clinical features, which occurred during relapse of the CADR, were detailed (group A1). In group B, the involved drugs were analyzed. The general framework of the study is presented in Fig. 1.

Ethical considerations

According to the advice of the President of the Ethic Committee of the University Hospital of Nancy, this study did not require any authorization from the Ethic Committee because it did not involve interventional methods. Information on the study was given to each patient by telephone before carrying out each survey.

Statistical analysis

Continuous data were expressed as mean or median values with standard deviation or range, nominal data were expressed as absolute and relative frequencies. Statistical analyses were performed with SAS v 9.1 software (Sas-Institute Inc, Cary, NC, USA).

Results

General analysis

Six hundred and thirty-seven negative drug RCH were analyzed from 349 patients (135 men, 214 women; mean age 47 years). One hundred and thirteen RCH (66 patients) did not meet the inclusion criteria or were lost to follow-up; among them, 13 deaths, not triggered by a CADR, occurred shortly after the RCH. Two hundred and eighty-three patients (524 RCH: 78 ST and 346 OPT) were questioned by the same investigator. In 76% of cases, the patient answered the questions, in 18%, a relative answered the questions, and in 6% of cases, the general practitioner (GP) answered the questions (Fig. 1).

Among 524 RCH, initial clinical features were maculopapular rash (55.1%) or eczematous rash (2.8%), urticaria (19%), angioedema (13.2%), DRESS (1.3%), fixed drug erythema (0.4%), acute generalized exanthematous pustulosis (0.3%), photo-allergy (0.1%), purpuric vasculitis (1.5%), pruritus (1.5%) and miscellaneous reactions (4.6%). Patients were questioned with a mean delay of 34 months (3–108 months) after the negative RCH.

In group A (134 RCH: 42 ST and 92 OPT in 113 patients), in spite of a negative RCH, subsequent intake of the drug was not tolerated in 12 cases in 10 patients (Table 1) and

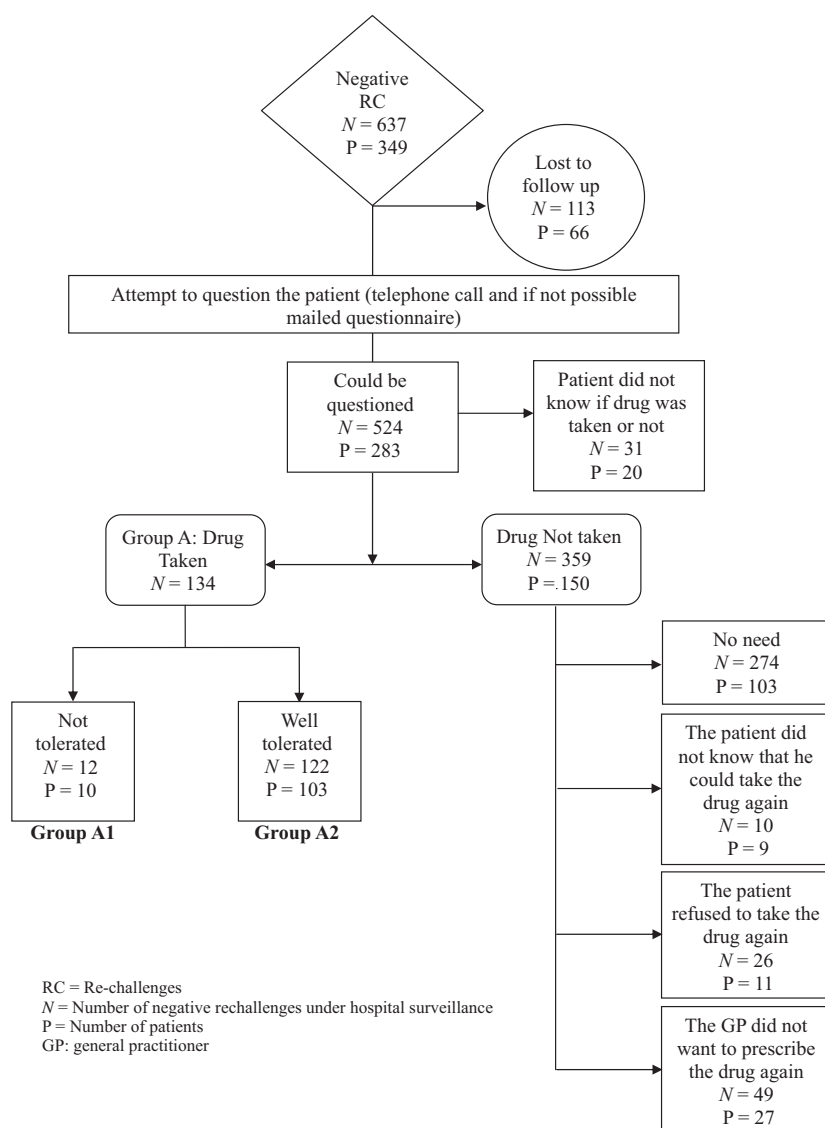


Figure 1 General framework of the study.

these patients were sub-classified into group A1. The NPV in these 134 RCH was 8.96% with CI 95% (4.48; 14.18%). A stomach ache was not interpreted as a positive provocation test. The drugs responsible were NSAIDs in two cases, corticosteroids (two cases), radio contrast media (RCM, two cases), chemotherapy (three cases), etanercept (one case), pregabalin (one case) and paracetamol (one case). Of these, in ten cases (seven OPT, three ST), symptoms were similar to those which occurred during the initial CADR: three immediate reactions (corticosteroids, paracetamol) and seven delayed reactions (chemotherapy, RCM, etanercept, pregabalin). In two cases, symptoms were different from those in the initial reaction. A patient who had angioedema because of naproxen reported rhinorrhea, cough, and sweats with diclofenac, the substitute drug chosen with the rheumatologist. Another patient who had pruritus with ketoprofen, followed by a

negative OPT with ketoprofen developed an eczematous reaction when taking the same NSAIDs (Table 2).

In 122 cases (group A2, 38 ST and 84 OPT), the drugs were well tolerated. Therefore, in this subpopulation, the long-term NPV of negative drug provocation tests under hospital surveillance was 91% (122/134). When the involved drugs were considered, good tolerance was observed in 23/24 (96%) cases with paracetamol, 1/4 with chemotherapy, 2/2 with vaccines, 6/6 with analgesics except paracetamol, 4/4 with antihypertensive drugs, 4/4 with proton pump inhibitors (PPIs), 20/22 (91%) with RCM, 16/18 (89%) with NSAIDs, 7/9 (78%) with systemic corticosteroids, 2/2 with local anesthetics and in 11/13 (84.6%) of the remaining cases with miscellaneous drugs. With some drug classes, subsequent re-intake was well tolerated, namely all 17 cases with beta lactam antibiotics and eight with other antibiotics (Table 3).

Table 1 Characteristics of 12 cases in 10 patients with positive subsequent re-challenge. One patient had a relapse in receiving cyclophosphamide, epirubicin, and fluorouracil

Drug classes	Sex	Age	Symptoms
Diclofenac	M	54	Sweats, rhinorrhea, cough
Betamethasone	F	68	Angioedema
Tixocortol Pivalate	F	42	Urticaria
Paracetamol	F	38	Angioedema
Ketoprofen	M	38	Eczematous rash
Cyclophosphamide	F	48	Eczematous rash
Epirubicin	F	48	Eczematous rash
Fluorouracil	F	48	Eczematous rash
Etanercept	M	56	Eczematous rash
Iopamidol	F	70	Maculopapular rash
Ioxaglate	F	44	Maculopapular rash
Pregabalin	F	60	Maculopapular rash

In group B (359 cases), we analyzed the reasons for absence of re-intake of the studied drug, despite a negative RCH. In 10 cases (nine patients), the patients did not understand that they were allowed to take the drug again. In 26 cases, 11 patients knew that they could take the drug but refused to do so. In 49 cases (27 patients), the GP was afraid and refused to prescribe the drug again. In most cases (274 cases), the patients (103/150) did not require any drugs from the time of the RCH to the telephone survey. The mean delay between the RCH and questioning was 33.9 months in the general population (group A + B + lost to follow-up), 33.9 months in group A vs 30.3 months in group B.

Sixty-six patients (18.9%) were eliminated for different reasons. Some patients were unable to be contacted because of erroneous telephone numbers; therefore, the questionnaire was sent to these patients for whom we had an address and only four responded. Twenty-three patients were lost to follow-up

and 16 patients had moved. Although we had a telephone number and address for an additional 13 patients, we were unable to reach them after three calls and messages left on their answering machines. One patient refused to answer and thirteen patients died (not because of drug hypersensitivity).

Miscellaneous information from the study

When asked about their tolerance to other drug classes, of the 283 patients, 250 had no reactions, 26 said they had another drug allergic reaction to another chemical class, and seven did not know how to answer this question.

Two hundred and twenty-three patients (79%) agreed to undergo drug skin tests again if required for another CADR, 23 would not undergo these tests again because it was too tiresome and 37 did not know.

For 88% of the patients drug skin tests and RC were useful for avoiding drugs suspected of being involved in their CADRs (116 answers, 41%) or helpful for anxious people who would refuse to take the recommended drug without proof of tolerance (101 answers). For RCM, 33 patients benefited from having a repeat checkup with radiological examinations. Skin tests and RCH did not have any interest for only 33 patients (11.6%).

Most of the patients had retained their hospitalization letter (202/283; 71.3%) with all the information concerning their CADR and recommendations about drugs which were forbidden or allowed after skin tests and provocation tests. Sixty-five patients did not know whether they had retained it, and 16 patients were sure that they had lost it.

Discussion

From this large study, which evaluated the outcomes of 637 RCH performed in 349 patients with a medical history of

Table 2 Comparison of studies regarding subsequent re-challenge after negative skin tests and provocation test under hospital surveillance

Studies		Patients having drug after RC				
Year	Author	Negative RC	Reactions	%	Drug class	
1996	Lopez-Serrano et al. (14)	197	NC	1	0.5	Beta lactams
1998	Hervé et al. (6)	NC	17	1	5.9	Amoxicillin
1998	Pichichero and Pichichero (7)	163	163	3	1.8	Beta lactams
1998	Macy (8)	146	93	3	3.2	Beta lactams
2003	Macy et al. (9)	568	568	65	11.4	Penicillins
2004	Bittner and Greenberger (10)	254	33	3	9.1	Beta lactams
2007	Ponvert et al. (11)	141	93	7	7.5	Beta lactams
2007	Demoly (4)	303	93	6	6.5	Beta lactams/nonsteroidal anti-inflammatory drugs
2009	Hershkovich et al. (12)	71	59	1	1.7	Beta lactams
2010	Demoly et al. (15)	457	118	9	7.6	Beta lactams
2010	Our results (beta lactams)	100	17	0		Beta lactams
2010	Our general results	637	134	12	9.0	Beta lactams and others drugs

RC, re-challenges; NC, not communicated.

%: percentage of relapse of the drug adverse reaction in patients having had a previous negative re-challenge under hospital surveillance.

Table 3 Tolerance and long-term NPV according to drug classes in group A (drug taken again)

Drug classes	Drugs re-challenges	Group A (taken)	% Taken	Not tolerated	% Not tolerated	Long-term NPV (%)
Beta lactams	100	17	17	0		
RCM	69	22	32	2	9	91
Miscellaneous drugs	67	13	19	2	15	85
NSAIDs	65	18	28	2	11	89
Other antibiotics	51	8	16	0		
Paracetamol (acetaminophen)	33	24	73	1	4	96
Systemic corticosteroids	33	9	27	2	22	78
Heparins	21	1	5	0		
Analgesics	15	6	40	0		
PPIs	12	4	33	0		
Antihypertensive drugs	11	4	36	0		
Local anesthetics	8	2	25	0		
Chemotherapy	4	4	100	3	75	
Vaccines	4	2	50	0		
Total	493	134	27	12	9	91

NSAIDs, nonsteroidal anti-inflammatory drugs; RCM, radio-contrast media; PPIs, proton pump inhibitors; NPV, long-term negative predictive value.

% taken: percentage of patients having taken the drug again after a negative drug re-challenge under hospital surveillance.

% not tolerated: percentage of patients having taken again the drug with a poor tolerance.

CADR suggesting cutaneous drug hypersensitivity, only 12 reactions (8.96%) were reported among 134 cases in which the studied drug had been subsequently retaken. Approximately 91% of patients with a negative RCH did not react again upon re-exposure. However, when considering beta lactam antibiotics, there are few data on positive subsequent re-intake after negative immuno-allergic investigations (skin tests and RCH) ranging from 0.5% to 11.4% of cases (4, 6–15). The details of these studies are shown in Table 2. The authors of prospective follow-up studies in children (11–12) suggested that when the diagnosis of beta-lactam allergy has been eliminated by negative skin test and RCH, the rate of re-sensitization is very low.

Recently, the NPV of RCH with RCM has been studied and the NPV was determined to be 96.6% with CI 95% (89.9–103.2) (13). The low NPV of skin tests for RCM has been previously reported (16, 17).

For the first time, we report on the long-term tolerance of many different drugs following a negative RCH. This long-term NPV of RCH depends on the considered drug and varies from 85% to 96% (Table 3) according to the different drug classes analyzed. With respect to chemotherapy, four treatments were administered after a negative RCH; unfortunately, three of these treatments were not tolerated, all in the same patient.

To explain false-negative RCH observed in 9% of cases, different hypotheses can be considered. Small dosages in a 1-day RC may be insufficient to induce clinical manifestations in patients who have mild sensitivity to a drug; however, this sensitization could induce a relapse of the CADR only when prolonged treatment is administered (1, 18). In delayed reactions, a 1-day readministration can be insufficient to elicit the reaction. Despite all, even in delayed reactions,

a 1-day readministration is usually sufficient to induce a relapse of the adverse drug reactions (2, 19) as observed in 14 cases among 27 positive provocation tests (2) or in 19 positive OPT (63.3%) performed in 30 patients with nonimmediate reactions to systemic corticosteroids (19). Co-factors such as concomitant medications, viral infections or physical exercise are not present during the RCH but can recur during subsequent re-intake of the drug (20). None of our patients reported a relapse of CADR after physical exercise. Re-sensitization upon re-exposure can appear and has been previously proved by re-testing patients. In fact, the rate of conversion was variable in different studies: from no re-sensitization (8, 10–12, 14, 21, 22) to more than 10% (7, 23–25). Beta lactams were the drug class used for these studies. Re-sensitization seems to be quite rare and is not the only procedure for explaining false-negative results in RCH. We did not re-test our nontolerant patients. Sensitization to drugs must also be regarded as a mechanism of breaking immune tolerance. In performing drug skin tests with progressively increased doses in IDT or RCH, over a short time, this gradual reintroduction of small doses of drug antigen could be responsible for the induction of temporary clinical unresponsiveness to drug antigens (4) and therefore, to false-negative RCH.

We could also consider improvements in this procedure; it would be interesting to evaluate the value of the following procedure: initial drug skin tests, then when negative, a 1-day RCH, followed 1 month later by re-administration of the drug tested during five consecutive days.

There is some bias in this study. Mild reactions could occur in group A, not considered by the patient which led to false-negative results. On the other hand, as we could not examine our patients when they had a relapse of their

CADR, false-positive results could also occur in anxious patients.

Skin tests followed by provocation tests in order to allow a drug seem to be a good procedure for managing patients suffering from nonsevere CADR, as the drug could be taken again and was well tolerated in 122 cases and in 79% (223/283) of patients answering the questionnaire. Moreover, most of the patients considered that the skin investigations were useful for them and would undergo such investigations again in the case of another CADR. An improvement in our educational management could diminish the number of patients afraid to retake the drug even after a negative RC or those who had lost their conclusion and recommendation letter. We emphasize that the GP also has to be educated concerning immuno-allergic investigations as 13.6% of patients did not retake the drug because their GP was afraid to prescribe it. Even when patients had a relapse of CADR, it was always a mild adverse effect.

For antibiotics and RCM, a great number of patients did not need to retake the drug which was tested by RCH. Therefore, the merits of immuno-allergic investigations for these drugs should be reassessed because the procedures are quite time consuming and expensive. However, we must also take into account that the molecules tested might be necessary when a life-threatening situation occurs and that these investigations may not be carried out in an emergency situation when prescription of the drug is essential.

Conclusion

The management of patients with suspected drug reactions should aim to avoid subsequent adverse reactions and provide safe alternative drugs. For that purpose, immuno-allergic investigations are useful. A negative RCH does not guarantee future tolerance of the drug, as 9.1% of our negative RCH and 9.1% of our patients had a relapse of their CADR, but that was nonsevere. A 1-day RCH could be completed followed by a 5-day long re-administration of the drug to confirm tolerance of the molecule.

We emphasize that patients and physicians need adequate documentation regarding drugs that must be avoided and those that are well tolerated. In addition, patients and physicians require education to permit the subsequent re-intake of drugs, which were well tolerated in almost 91% of cases with a history of CADR, and who without these immuno-allergic investigations would possibly not take many classes of drugs, useful for them.

Conflict of interest

None.

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