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Original article

Incidence of systemic reactions to skin tests and drug challenge tests

L'incidence des réactions systémiques aux tests cutanés et aux tests de provocation

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Abstract

Study objective. – Localised and systemic immediate-type reactions during allergological in vivo tests for drugs are a rare occurrence. However, in high-risk patients, immediate intensive care support is required. We sought to evaluate the risk of systemic reactions induced by skin tests and drug challenge tests.

Patients and methods. – We investigated all immediate-type reactions that occurred during allergological testing in the outpatient allergeo-anaesthesia unit of the Cluj Clinical Emergency County hospital from 2007 until August 2017 in order to identify patients presenting localised and systemic immediate-type hypersensitivity reactions.

Results. – Drugs were tested in 2139 patients using in vivo allergological tests. In total, 261 patients presented positive skin prick-tests and 535 presented positive intradermal tests. One patient presented grade II anaphylaxis during intradermal testing with antibiotics (amoxicillin) and one patient presented grade III anaphylaxis induced by intradermal testing of midazolam. We performed 553 drug challenge tests. Twenty-nine patients presented positive drug challenge tests. One patient presented grade III anaphylaxis during a drug challenge test with etoricoxib. Grade III anaphylaxis was also induced in a patient challenged with clindamycin. Four of 29 patients with a positive drug challenge test developed grade II anaphylaxis, while 23 of 29 presented grade I anaphylaxis. Two of 29 positive drug challenge test patients experienced more severe reactions during testing compared with previous hypersensitivity reactions, while 8 patients presented less severe reactions.

Conclusion. – Though low, the risk of induction of severe systemic reactions during allergological skin tests and drug challenge tests nevertheless remains present.

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Keywords: Drug allergy; Allergological tests; Skin tests; Drug challenge tests; Systemic reactions

Résumé

But de l'étude. – Les réactions localisées et systémiques de type immédiat survenant lors du bilan allergologique in vivo pour divers médicaments sont des événements rares. Cependant, chez les patients à haut risque, un accès immédiat aux soins intensifs est nécessaire. Nous voulons évaluer le risque d'induire des réactions systémiques lors des tests cutanés et des tests de provocation.

Patient et méthodes. – Nous avons étudié toutes les réactions de type immédiat survenues lors du bilan allergologique dans l'unité d'allergologie et d'anesthésie ambulatoire de l'hôpital clinique d'urgence du département de Cluj, de 2007 jusqu'au mois d'août 2017, afin d'identifier les patients présentant des réactions d'hypersensibilité de type immédiat localisée et systémique.

Résultats. – Des médicaments ont été testés sur 2139 patients en utilisant le bilan allergologique in vivo. Au total, 261 patients ont présenté des prick-tests positifs et 535 patients ont présenté des tests intradermiques positifs. Un patient a présenté une anaphylaxie de grade II lors d'un test intradermique à des antibiotiques (amoxicilline) et un patient a présenté une anaphylaxie de grade III induite par un test intradermique au

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midazolam. Nous avons effectué 553 tests de provocation. Vingt-neuf patients ont présenté des tests de provocation positifs. Un patient a présenté une anaphylaxie de grade III survenue lors d'un test de provocation à l'étoricoxib. Une anaphylaxie de grade III a été également induite chez un patient testé à la clindamycine. Quatre sur 29 patients présentant un test de provocation positif ont développé une anaphylaxie de grade II et 23 sur 29 ont présenté une anaphylaxie de grade I. Deux sur 29 patients présentant des tests de provocation positifs ont présenté des réactions plus sévères au cours des tests comparés aux réactions d'hypersensibilité précédentes et 8 patients ont présenté des réactions moins sévères. **Conclusion**

Bien que rare, le risque d'induire des réactions systémiques sévères lors des tests cutanés allergologiques et des tests de provocation, est toujours présent.

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Mots clés : Allergie aux médicaments ; Bilan allergologique ; Tests cutanés ; Tests de provocation ; Réactions systémiques

1. Introduction

Drug hypersensitivity reactions are frequent reasons for patients' presentation in allergy centers. The symptoms of anaphylaxis can involve any organ, the most commonly affected being the skin (in 88% of cases). Hypotension and severe reactions are most likely to be associated to drugs [1,2].

The diagnosis of anaphylaxis include history and physical examination. History may be inconclusive in some cases such as anaesthesia when multiple drugs are administered in a very short period of time or when patients take different drugs simultaneously.

To assess IgE-mediated hypersensitivity reactions, skin testing including skin prick-tests and intradermal tests are performed. For drug-induced anaphylaxis skin prick-test is performed usually with undiluted drug. If negative, intradermal test with increasing concentration of drug is performed due to the potential risk of inducing a systemic reaction. Skin prick-test has been widely used and has been considered a safe procedure, the rate of systemic reaction after the skin prick-test being 0.02–0.07% in the previous studies [3]. The frequency of systemic reactions after beta-lactam skin tests varies from 0.1% to 2% in a study conducted by Torres et al. [4].

For most drugs, a negative skin test does not exclude an allergic reaction. Therefore, a drug provocation test can complement the diagnosis. A high risk of inducing another hypersensitivity reaction is present in drug provocation test so for this reason this is primarily indicated in patients with a low clinical suspicion of drug allergy and for patients in which is important to find alternatives to the culprit drug [1]. Facilities for continuous monitoring should be immediately available together with a well-trained staff and emergency drugs. The more rapidly anaphylaxis develops; the more likely is to be a severe reaction.

In the last years, in order to reduce the risk of inducing systemic hypersensitivity reactions during in vivo tests (skin prick-test, intradermal test and drug challenge test), international guidelines reduced drug concentrations used for testing and recommended progressive testing to avoid fatal anaphylactic reactions [1].

In this article, we want to evaluate the risk of inducing systemic reactions during in vivo allergological tests and to quantify the rate of systemic reactions caused by allergological testing in our allergeo-anesthesia department.

2. Patients and methods

In our outpatient allergeo-anaesthesia unit of the Clinical Emergency County hospital Cluj, we investigated all immediate-type reactions that occurred during allergological tests for drugs (antibiotics, non-steroidal anti-inflammatory drugs, anesthetic drugs) from 2007 to August 2017.

After giving their informed consent, patients with positive history of antibiotic anaphylactic reactions, hypersensitivity reactions to non-steroidal anti-inflammatory drugs and perioperative anaphylactic reactions were tested. The time between the hypersensitivity reaction and testing was usually 4–6 weeks. The patients were tested in a safe environment with available equipment for monitoring, emergency drugs and with access to a well-trained anesthetist.

We performed skin prick-tests, intradermal tests and drug challenge tests to antibiotics, non-steroidal anti-inflammatory drugs and local anesthetics. For general anesthetic drugs, we performed only skin tests. Intradermal test was performed only if a negative skin prick-test was present and if both skin tests were negative, we proceed to drug provocation test. In this situation, the patient had venous access established before the beginning of the test and continuous monitoring during the test and 6 hours after. Drug concentrations used for skin testing to antibiotics and anesthetic agents follow international guidelines and are presented in Tables 1 and 2 [5–7]. For non-steroidal anti-inflammatory drugs, skin prick-test is performed with undiluted drug and for intradermal test, solutions of 1/100 are used. Skin tests are performed as a part of incremental exposure to drug during drugs provocation test for non-steroidal anti-inflammatory

Table 1
Antibiotic concentrations for skin tests [5,6].

Antibiotic	SPT	IDT
Peniciline	10,000 IU/mL	10,000 IU/mL
Amoxiciline	20 mg/mL	20 mg/mL
Ampiciline	20 mg/mL	20 mg/mL
Cefuroxime	20 mg/mL 2 mg/mL	2 mg/mL
Ceftriaxone	20 mg/mL 2 mg/mL	2 mg/mL
Imipenem	10 mg/mL(5/5 mg/mL)	1 mg/mL
Ciprofloxacin	1 mg/mL	10 µg/mL
Gentamicine	40 mg/mL	400 µg/mL
Vancomicine	0.1 µg/mL	0.1 µg/mL

SPT: skin prick-test; IDT: intradermal test.

Table 2
Anesthetic agents concentration for skin tests [5,6,7].

Drug	SPT (mg/mL)	IDT
Atracurium	1	10 µg/mL
Rocuronium	10	50 µg/mL
Succinylcholine	10	100 µg/mL
Mivacurium	0.2	2 µg/mL
Fentanyl	0.05	5 µg/mL
Remifentanyl	0.05	5 µg/mL
Sufentanyl	0.005	0.5 µg/mL
Midazolam	5	250 µg/mL
Etomidate	2	200 µg/mL
Propofol	10	1 mg/mL
Tramadol	50	500 µg/mL
Pethidine	25	2.5 µg/mL
Morphine	1	10 µg/mL

SPT: skin prick-test; IDT: intradermal test.

drugs. For those drugs in which parenteral solutions are not available in our country, we performed only skin prick-test with powder drug suspension (ground table and physiological saline solution) according to international recommendations [8].

Drug challenge test (for antibiotics, non-steroidal anti-inflammatory drugs and local anesthetics) was performed following international guidelines, orally or subcutaneously in patients in which clinical suspicion was low and in patients where it was essential that alternatives to culprit drug to be identified [8].

We defined the systemic reactions as any signs and symptoms other than a local reaction thought to be secondary to allergological tests. Grading the severity of reactions induced by allergological tests used the modification of Ring and Messmer grading scale as shown in Table 3 [9,10]. We considered grade I anaphylaxis the presence of mucocutaneous signs, grade II anaphylaxis the presence of mucocutaneous signs and symptoms concerning respiratory system (rhinorrhea, hoarseness or dyspnoea), cardiac (tachycardia/hypotension) or gastrointestinal system (cramps, nausea, vomiting). Grade III anaphylaxis was

considered when respiratory symptoms like laryngeal edema, bronchospasm or cyanosis; cardiovascular symptoms like shock or gastrointestinal symptoms like vomiting or diarrhea were present. We diagnosed grade IV anaphylaxis when respiratory or cardiovascular arrest was present together with or without mucocutaneous signs.

3. Results

During 2007 until August 2017, we have tested, in our allergeo-anesthesia unit, 2139 patients. We have tested patients with positive history of drug allergy (antibiotics and non-steroidal anti-inflammatory drugs) and surgical patients with positive history of perianesthetic drug hypersensitivity. Each patient was tested for the culprit drug and alternatives drugs were also tested.

In total, 826 patients presented positive in vivo tests; 261 patients presented positive skin prick-test and 535 patients presented positive intradermal test. We have performed 553 drug provocation tests with 29 positive tests.

One patient with positive history of asthma and anaphylactic shock to ampiciline and grade II anaphylaxis to cefuroxime and fluconazole being skin tested to antibiotics presented positive intradermal test to amoxiciline (20 mg/mL). Twenty minutes later, the patient developed facial urticaria, ocular pruritus and dyspnoea (grade II anaphylaxis) which were treated with inhaled bronchodilators, intravenous hydrocortisone and oral antihistamine drugs (loratadine). The patient was admitted to the hospital for further monitoring and was discharged after 12 hours free of any symptoms.

One patient, presenting anaphylactic shock during a procedural sedation with midazolam for an upper gastrointestinal tract endoscopy, developed respiratory manifestations (grade III anaphylaxis) during minutes after being skin tested for midazolam. In this case, skin prick-test for midazolam was negative and intradermal test at a dose of 250 µg/mL produced

Table 3
Severity scale for classification of immediate type hypersensitivity reactions.

Grade	Skin and subjective generalized symptoms	Abdomen	Respiratory tract	Cardiovascular
I	Itching Flushing Urticaria Angioedema	–	–	–
II	Itching Flushing Urticaria Angioedema	Nausea Cramps Vomiting	Rhinorrhea Hoarseness Dyspnoea	Tachycardia (rise > 20/min) Hypotension (fall > 20 mm Hg systolic) Arrhythmia
III	Itching Flushing Urticaria Angioedema	Vomiting Diarrhea	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Itching Flushing Urticaria Angioedema	Vomiting Diarrhea	Respiratory arrest	Cardiovascular arrest

Worm et al. (modified from Ring and Messmer, 1977) [9], Mertes et al. [10].

severe bronchospasm with desaturation (peripheral oxygen saturation of hemoglobine was less than (90%). Intravenous adrenaline (100 µg) and supplementary oxygen were rapidly administered. Intravenous hydrocortisone and oral antihistamines were also administered. The patient was admitted to the intensive care unit where inhalatory adrenaline was further needed together with continuation of antihistamine therapy and hydrocortisone.

Thus, one patient (0.04%) presented grade II anaphylaxis during intradermal testing to amoxiciline and one patient out of 2139 patients (0.04%) developed grade III anaphylaxis during intradermal testing for midazolam.

Twenty-nine (5.24%) patients out of 553 tested presented positive drug challenge test.

One patient developed grade III anaphylaxis with cardiovascular symptoms requiring adrenaline administration and intensive care unit admission. Etoricoxib (Arcoxia), a selective cyclo-oxygenase 2 inhibitor, was tested using skin prick-test; this being negative, a drug provocation test was initiated. After the first dose of 5 mg orally, the patient presented hypotension, not responding to fluid administration and ECG modification – sinus tachycardia, ventricular ectopic beats and ST segment depression in anterior and lateral leads. The patient was admitted in the intensive care unit for monitoring and required continuous adrenaline infusion for 24 hours. Antihistamine therapy and hydrocortisone were also administered. Continuous ECG monitoring did not reveal any signs of further myocardial ischemia. The patient stabilized and was discharged from intensive care unit after 48 hours.

Another patient with history of grade III anaphylaxis to amoxiciline and grade II anaphylaxis to metamizole being challenged to oral clindamycin developed grade III anaphylaxis. First dose consisted of 30 mg oral clindamycin and 30 minutes later, the second step dose of 45 mg was administered. After another 30 minutes, the patient developed severe dyspnoea with bronchospasm, flushing and agitation. Inhaled adrenaline (1 mg in 5 mL of normal saline), intravenous hydrocortisone, bronchodilators and oral antihistamine drugs were initiated and the patient was admitted to intensive care unit for monitoring and further treatment. The patient stabilized, respiratory function improved and did not require any further treatment. He was discharged after 12 hours.

Thus, two patients (6.89%) developed grade III anaphylaxis requiring intensive treatment and monitoring during drug challenge test.

The rest of 27 patients with positive drug challenge test presented grade I and II severity reactions, 4 (13.79%) patients presented grade II anaphylaxis and 23 (79.31%) patients presented grade I anaphylaxis. Two patients out of 29 positive challenge test patients developed more severe allergic reactions than the initial hypersensitivity episode and 8 patients experienced less severe reactions during challenge compared with the history. All the patients were monitored continuously during the next 6 hours and were discharged free of symptoms. Individual characteristics of positive drug challenge patients are listed in Table 4.

Agents responsible for inducing positive drug challenge tests are presented in Table 5.

4. Discussion

Skin tests are useful tests for diagnosis of IgE-mediated reactions and generally, they are considered very safe. Systemic manifestations of anaphylaxis during allergological tests could be an occurring event in very sensitive patients, the risk being higher with intradermal test and even higher with the drug challenge test.

Skin testing is associated with non-fatal systemic reactions and previous studies have found a risk of less than 0.02% [11]. Sellaturay et al. report a rate of systemic reactions induced by skin prick-testing for allergy of 0.07% to food, aeroallergen and drugs (mostly antibiotics) [3]. They define systemic reactions as grade I – mild (localized cutaneous symptoms, urticaria, angioedema, oral pruritus), grade II – mild (generalized cutaneous symptoms, urticaria, angioedema), grade III – mild (grade I or II plus gastrointestinal symptoms or rhinoconjunctivitis), grade IV – moderate (mild laryngeal edema, mild asthma), grade V – severe (pronounced dyspnoea, hypotensive symptoms). In our allergeo-anesthesia department, we have tested using skin prick-tests only drugs (antibiotics, local and general anesthetics, non-steroidal anti-inflammatory drugs) and we do not report systemic reactions during skin prick-testing.

Regarding intradermal test, Bagg et al. in a one-year prospective study, reports a rate of systemic reactions (defined as any sign or symptom other than a local reaction thought to be secondary to skin test) to venoms and aeroallergens of 3.4% [12]. In our center, 0.04% of the patients tested with intradermal skin test for drugs developed grade III anaphylaxis and 0.04% developed grade II anaphylaxis. Swender et al., in a study which encompassed 13 years and almost 50,000 patients visits for skin tests to drugs, venoms, environmental allergens and aeroallergens, identified 0.02% of epinephrine administration during skin prick-tests and 0 for intradermal testing. In this study, systemic anaphylaxis was defined as any systemic reaction treated with epinephrine or fulfilling criteria for diagnosing anaphylaxis as set by World Allergy Organization: an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur: diffuse erythema, pruritus, urticaria and/or angioedema; bronchospasm; laryngeal edema; hypotension; cardiac arrhythmias; feeling of impending doom; unconsciousness and shock. Other earlier or concomitant signs and symptoms can include itchy nose, eyes, pharynx, genitalia, palms, and soles; rhinorrhea; change in voice; metallic taste; nausea, vomiting, diarrhea, abdominal cramps, and bloating; light-headedness; headache; uterine cramps; and generalized warmth [13,14].

Discrepancies in the reported incidence for systemic reactions induced by skin tests may result from the definitions used for systemic reactions.

Liccardi et al. highlights that in polysensitized patients, simultaneous exposure to multiple allergens using a skin prick-test model induces additive histamine release from cutaneous mast cells compared to exposure to a single allergen and

Table 4
Individual characteristics of positive challenge test patients.

Patient	Age (years)	History severity grade	Reported drug allergy	Challenge agent	Challenge reaction severity grade
1	65	I	Metamizole, ibuprofen	Etoricoxib	III
2	60	I	Penicilin	Cefuroxime	I
3	72	III	Metamizole	Etoricoxib	II
4	60	I	Metamizole	Etoricoxib	I
5	69	I	Trimethoprim/sulfamethoxazol	Cefuroxime	I
6	50	I	Metamizole, diclofenac	Etoricoxib	I
7	38	III	Ibuprofen, diclofenac	Etoricoxib	I
8	56	I	Peniciline, ampiciline	Cefuroxime	I
9	33	I	Clarithromycine	Ceftriaxone	I
10	55	I	Ampicilie, oxaciline, ibuprofen	Etoricoxib	I
11	58	II	Peniciline, ciprofloxacin, cefuroxime	Cefotaxime	I
12	19	I	Peniciline, imipenem	Ceftriaxone	II
13	40	I	Ampiciline, gentamicine, metamizole	Clarithromycine	I
14	27	I	Peniciline	Clarithromycine	I
15	46	III	Oxaciline, ampiciline, cefuroxime, metamizole	Etoricoxib	I
16	68	III	Peniciline, metamizole, lidocaine	Ketorolac	I
17	66	III	Metamizole, peniciline	Cefuroxime	I
18	43	III	Aspirin, metamizole	Etoricoxib	I
19	50	I	Amoxiciline, ampiciline	Cefuroxime	I
20	44	I	Peniciline, gentamicin, lidocaine	Lidocaine	I
21	42	I	Peniciline, lidocaine	Lidocaine	I
22	59	I	Metamizole	Etoricoxib	I
23	45	I	Ketorolac, metamizole	Nimesulide	I
24	48	I	Ibuprofen, ketorolac	Aspirin	I
25	44	I	Peniciline, metamizole	Etoricoxib	I
26	38	III	Ceftriaxone, cefuroxime, metamizole	Doxycycline	II
27	18	I	Metamizole, ibuprofen	Etoricoxib	I
28	49	III	Amoxiciline, metamizole	Clindamycine	III
29	59	II	Metamizole, celecoxib	Etoricoxib	II

Table 5
Agents responsible for inducing positive drug challenge tests.

Agents	Patients	Patients (%)
Antibiotics	12	41.37
Beta-lactams	8	27.58
Clarithromycine	2	6.89
Doxycycline	1	3.44
Clindamycine	1	3.44
Non-steroidal anti-inflammatory	14	48.27
Aspirin	1	3.44
Lidocaine	2	6.89

emphasizes the synergic effect of several allergens in the development of systemic reactions [15]. In our center, patients were exposed to at least 6–7 substances simultaneously during prick-testing. We do not report systemic reactions during skin prick-test but we report one polysensitized patient, with asthma history and anaphylaxis induced by antibiotics, skin tested for antibiotics (prick-test with undiluted substance and intradermal test with dilution of the drugs) who presented positive intradermal test to one alternative substance and developed grade II anaphylaxis 20 minutes later. We did not test venoms and environmental allergens.

Although challenge tests are performed in low-risk patients, they could cause adverse reactions and safety is of major importance. In our center, where drug challenge tests to antibiotics,

local anesthetics and non-steroidal anti-inflammatory drugs were performed, we report a rate of positive challenge test of 5.24% while Mawhirt et al. in a 5 year review of patients with hypersensitivity reactions induced by antibiotics challenged to antibiotics reported a rate of 8.9% [16]. In the same study 13% of patients with positive challenge test to antibiotics developed grade III anaphylaxis, as defined by Sampson et al. [17], 25% developed grade II reactions (mucocutaneous, gastrointestinal or respiratory involvement) and 47% presented grade I reactions (cutaneous signs only). In our study from 29 patients with positive challenge test to antibiotics, local anesthetics and non-steroidal anti-inflammatory drugs 6.89% presented grade III reactions, 13.79% presented grade II reactions and 79.31% developed grade I reactions during challenge. These differences may also be explained by the use of distinct definitions for systemic reactions.

In our study, we observe a high number of patients reacting to anti-cyclo-oxygenase 2. Our patients describing an adverse effect after non-steroidal anti-inflammatory drugs use were anxious and stressed about the following diagnostic procedures. Most of the patients needed an immediate treatment for their underlying condition but they refused to be exposed to drugs from the same class as the causative agent, especially anti-cyclo-oxygenase 1. An anti-cyclo-oxygenase 2 agent was tested instead and this can explain the amount of patients reacting to this drug class.

5. Conclusions

The risks of systemic reactions associated with skin tests and drug challenge test are important to be recognized.

These tests should be performed under specialized supervision where resuscitation facilities are available and where the early signs of severe anaphylaxis could be rapidly identified.

Immediate identification of systemic hypersensitivity reaction and rapid intervention could prevent aggravation and fatalities.

Disclosure of interest

The authors declare that they have no competing interest.

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