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CLINICAL REPORT

Cutaneous Adverse Drug Reactions Seen at a University Hospital Department of Dermatology

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Patients with suspected cutaneous adverse drug reactions are often referred to allergy clinics or departments of dermatology for evaluation. These patients are selected compared with patients identified in prospective and cross-sectional studies of hospital populations. This explains the observed variation in prevalence of specific reactions and of eliciting drugs. This study investigated the prevalence of cutaneous adverse drug reactions in a university hospital department of dermatology that is specially focused on allergy. An 8-month survey was carried out during the period April–December 2003. Consecutive patients suspected of having cutaneous adverse drug reactions during this period were examined by dermatologists and investigated. Drug imputability was assessed in the 194 patients included; 33.5% had an exanthema with certain or likely drug imputability. Urticaria and local reactions at injection sites were the most frequent reactions (25% and 18.8%, respectively). β-lactam antibiotics, extracts for desensitization and insulins were the main drug groups involved, and accounted for 22.8%, 17.1% and 14.2%, respectively, of the reactions. Extracts for desensitization and insulins elicited more reactions than expected. This probably reflects the referral pattern to an allergy clinic. ***Key words: cutaneous adverse drug reaction; drug allergy; drug eruptions; epidemiology; pharmaco-vigilance.***

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Cutaneous adverse drug reactions (CADR) can be defined as noxious, unintended morphological skin changes with or without systemic involvement, developed after local or systemic administration of drugs in dosages commonly used for prevention, diagnosis or treatment of disease or modification of physiological functions, in accordance with the World Health Organization's general definition of adverse drug reactions (ADR) (1). The spontaneous reporting of ADR is inconsistent (2) and furthermore varies between countries, as does drug use, illustrated by the variations in antibiotics sales in the European Union (EU) (3). Narrow-spectrum penicillins are used widely in the Scandinavian member states in contrast to the rest of the EU. Broad-spectrum penicillins, macrolides, lincosamides, and trimethoprim are used much less in the Scandinavian countries than in the rest of the EU.

National/regional studies are necessary for the mapping of the pattern and prevalence of CADR, as is studies aiming to determine the extent of ADR in the various contexts of general practice, hospital departments, and hospital populations.

Studies on the epidemiology of CADR have recently been performed in hospital populations (4, 5). No recent study on the occurrence of CADR in consecutive in- and out-patients in a dermatological university clinic exists from our part of the world.

This study aims to describe the occurrence of diagnosed drug eruptions seen in the department of dermatology and its allergy clinic (Allergy Centre).

PATIENTS AND METHODS

This retrospective study on consecutive patients suspected of CADR was carried out in the Allergy Centre and Dermatology Department at Odense University Hospital, University of Southern Denmark between April and December 2003. The department serves as a tertiary referral centre and sees patients referred by hospitals, practising dermatologists and general practitioners in Funen and the Southern part of Jutland (approximately 1.3 million inhabitants). The department sees approximately 7100 patients each year and has a specialized allergy clinic attached. In this 8-month period 194 in- and out-patients suspected of having CADR were examined by dermatologists. If CADR was suspected, the patient was referred to the allergy clinic after a primary visit to the Department of Dermatology, and investigated by blood tests relevant to the specific skin disorder, skin prick tests, intradermal tests, patch tests and drug challenge tests. To assure that all relevant patients were included in the analysis a computer-based search was performed for patients with the following diagnoses: Exanthema medicamentale (T88.6), Anaphylaxis due to drug allergy (Z88.9), Drug allergy without specification (T88.7), History of penicillin allergy (Z88.0), and History of drug allergy (Z88.9). Of the 194 patients, 46 had escaped primary referral from the Department of dermatology to the Allergy Centre and were included following the computerized search. Finally, the history and clinical presentation were evaluated in a retrospective determination of the imputability of each drug as the possible culprit. Imputability analysis was performed as described by Moore et al. (6). Drug imputability of the cases was described as "likely" (= certain or likely), "possible" or "unlikely". Cases

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with the imputability score of "likely" were defined as drug induced and included for further analysis. In the 46 patients who escaped primary referral, drug imputability was established retrospectively from history, para-clinical investigations, but without *in vivo* allergological tests.

Specific IgE was measured when applicable using CAP Pharmacia (Stockholm, Sweden). Basophil histamine release (HR) (RefLab, Copenhagen, Denmark) (7) was measured for all suspected drugs. Skin prick tests (SPT) were performed using commercially available formulations of the suspected drugs. SPT was performed in concentrations of 1:1 except in cases of suspected type 1 reactions where dilutions up to 1:1000 were used. Intradermal tests (IDT) were performed in concentrations of 1:1000–1:1 of commercially available sterile formulations for injections of the suspected drugs. Dilutions were made in commercial vials, and IDT was performed on the lateral side of the upper arm. Histamine HCl 10 mg/ml (ALK-Abelló, Hørsholm, Denmark) was used as positive control and isotonic saline was used as negative control. SPT and IDT were read according to the guidelines of The European Academy of Allergology and Clinical Immunology (EAACI) (8). Drug challenge test (DCT) was performed when all afore-mentioned tests were negative in dilutions of 1:1000–1:1 of one therapeutic dosage, unless contraindicated (9). The DCT was considered positive upon recurrence of symptoms of the initial reactions.

Patch tests were performed using standard technique with Finn Chambers on Scanpore (Epitest Ltd Oy, Tuusula, Finland & Alpharma AS, Oslo, Norway) and pure drugs in 10% pet./aq./eth. (Chemotechnique, Malmö, Sweden). Drugs not available in this formulation were tested using commercially available formulations of the drugs in 30% pet./aq./eth. (10). A number of drugs were investigated for cross-reactivity using patch test panels of: β-lactam antibiotics, cycline antibiotics, quinolones, macrolides, non-steroidal anti-inflammatory drugs (NSAIDs) and benzodiazepines, as suggested in an unpublished study protocol by Barbaud et al. (10). Patch tests were read on day 3 and day 5–7 according to the International Contact Dermatitis Research Group (ICDRG) recommendations (11).

Statistical analysis was performed using Fisher's exact test. Level of significance was set to 5%.

RESULTS

In the study period 4706 individual patients were seen in the Department of Dermatology and its allergy clinic. A total of 194 cases of possible CADR were evaluated and 65 (33.5%) diagnosed as such (Fig. 1), yielding a prevalence of 1.38% among total referrals to the Department of Dermatology. The mean age of the patients with CADR was 52 years (range 8–86 years). The sex ratio (F/M) was 2.3.

The clinical classification of the 65 cases is shown in Table I. Urticaria, local reactions, and a combination of urticaria and angioedema were the most common reactions seen but a variety of other reactions were also observed.

Of the eliciting drugs, β-lactam antibiotics, extracts for desensitization (timothy: Phleum pratense; ALK-Abelló) and insulins were the most frequent eliciting agents (Table II). Reactions to extracts for desensitization with grass were generalized in 6/11 cases with urticaria, and anaphylaxis in 1 case. The remaining 5 cases were local reactions with swelling, redness and itch. Three of 11 patients reacted within minutes and 6/11 within a few hours following injection. None of the generalized immediate reactions took place in the Allergy Centre. The patients experiencing adverse reactions to extracts for desensitization were all referred for investigation from general practitioners. In two cases the latency period was not recorded. All reactions to insulins were local and described as rash or redness and itch developed within a few hours after injection of insulin.

The culprit drug was not identified in 5 "likely" cases of CADR (7.8%): 1 patient with autoimmune

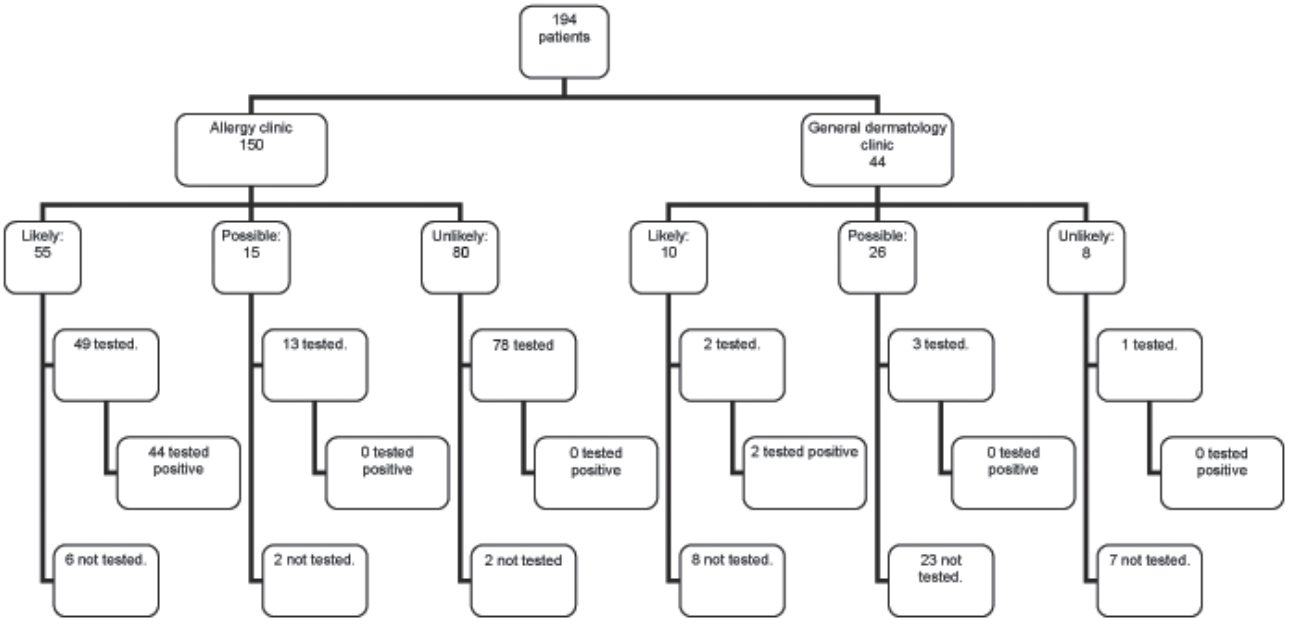

Fig. 1. Drug imputability in 194 patients evaluated for cutaneous adverse drug reactions.

Table I. *Cutaneous adverse drug reactions by diagnosis*

Clinical diagnosis	No. of patients (%)	Eliciting drugs and number of cases
Urticaria	17 (26.2)	Amoxicillin 1, Ceterizine 1, Diclofenac 2, Dicloxacillin 1, Grass extract 5, Hepatitis B vaccine 1, Insulin 3, Penicillin 3
Local reaction	12 (18.5)	Grass extract 4, Heparins 1[b], Insulin 6, Lidocaine 1
Urticaria & angioedema	7 (10.8)	Amoxicillin 1, ASA 1, Ciprofloxacin 1, Ibuprofen 1, Penicillin 2, Trandolapril 1
Rash (unspecified)[a]	5 (7.7)	Grass extract 1, Allopurinol 1, Ampicillin 1, Penicillin 2,
Maculo-papular rash	5 (7.7)	Allopurinol 1, Ampicillin 1 (/gentamicin), Ibuprofen 1, Pivampicillin 1, Spironolactone 1
Anaphylaxis	5 (7.7)	Enalapril 1, Excipients 1, Grass extract 1, Unknown 2,
Angioedema	4 (6.2)	Acetylsalicylic acid 2, Insulin 1, Bupropion 1
Periorbital dermatitis	2 (3.1)	Phenylephrine
Psoriasis	2 (3.1)	Peginterferon α-2/Ribaverin 1, Perindopril 1
Eczema	1 (1.5)	Oxcarbazepine
Gingival hyperplasia	1 (1.5)	Cyclosporine
Lupus erythematosus, systemic	1 (1.5)	Carbamazepine
Subacute cutaneous lupus erythematosus	1 (1.5)	Esomeprazol
Purpura	1 (1.5)	Cytarabin/Mitocantion
Bullous pemphigoid	1 (1.5)	Penicillin[b]
Total	65	

[a]Patient unable to specify/not clear from history.
[b]Previously published as case reports (22) and (24), respectively.

urticaria had urticaria following intake of cetirizine (UCB Pharma, Brussels, Belgium) and desloratadine (Schering-Plough Corp., New Jersey, USA) tablets on several occasions, but did not react to DCT with the liquid formulation of cetirizine or to any of the excipients upon skin test or DCT. Two of the patients referred had anaphylaxis with hypotension during general anaesthesia. One had elevated s-tryptase (113 μg/ml, normal baseline), the other had normal value, eosinophils were not measured. All skin tests and DCT for antibiotics were negative. DCT for neuromuscular blocking agents and anaesthetics were not performed. One case of maculo-papular rash had reactions upon DCT with ampicillin and gentamicin, but did not want the procedure repeated with the single drugs so the culprit could be identified. A patient with chronic hepatitis without any history of previous psoriasis was treated with peg-interferon α-2a and ribavirin and developed a psoriasiform reaction, peripheral and tissue eosinophilia and had a skin biopsy showing changes compatible with a drug reaction.

Most frequently occurring disorders other than the CADR were hayfever/atopy, type II diabetes, and contact allergy occurring in 13, 8 and 8 patients, respectively. Contact allergies were found to nickel in 7 patients, and to fragrance mix, thimerosal, p-phenylendiamine, colophony, Euxyl K400, methyldibromo-glutaronitril, mix of quinolones, epoxy resin, and ethylenediamine in one case each.

Table III lists the different findings for patients with and without CADR: the number of positive reactions of each test modality, the number of tests performed,

Table II. *Drug groups implicated in cutaneous adverse drug reactions (CADR) in 65 patients*

Drug	No. of CADR (%)
β-lactam antibiotics	16 (22.8)
Extracts for desensitization	12 (17.1)
Insulins	10 (14.2)
ASA & NSAIDs	7 (10.0)
Excipients	6 (8.5)
ACE-inhibitors	3 (4.2)
Allopurinol	2 (2.8)
Phenylephrine	2 (2.8)
Anti-convulsives	2 (2.8)
Antihistamines	1 (1.4)
Bupropion	1 (1.4)
Cyclosporine	1 (1.4)
Cytokines	1 (1.4)
Diuretics, aldosterone antagonist	1 (1.4)
Heparins	1 (1.4)
Local anaesthetics	1 (1.4)
Proton pump inhibitor	1 (1.4)
Quinolones	1 (1.4)
Steroids	1 (1.4)
Vaccines	1 (1.4)
Total	71

ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drugs.

Table III. *Positive tests in drug allergy investigation on patients with cutaneous adverse drug reactions (CADR) and non-CADR*

	No. of positive tests (= patients)/ No. performed tests (= patients)	
Test	CADR	Non-CADR
Histo-pathology, diagnosis supported	6 / 9 (28.5%)	7 / 12 (33.3%)
Histo-pathology, tissue eosinophilia	7 / 9 33.3%	4 / 12 19.0%
Peripheral eosinophils	2 / 9 (5.2%)	10 / 29 (34.4%)
S-tryptase[a]	3 / 7 (14.2%)[b]	0 / 14 (0%)

[a]Baseline tryptase was normal in all patients
[b]1 anaphylaxis during anaesthesia, 1 anaphylaxis and urticaria during DCT with diclofenac in a patient with negative DCT to ASA, 1 urticaria to penicillin in a patient with hereditary angioedema treated with C1-esterase inhibitor.

Table IV. *Investigation of positive allergy tests in cutaneous adverse drug reactions (CADR)*

	CADR		Non-CADR	
Test	No. of positive tests/ No. performed	No. of test-positive patients/ No. of patients tested	No. of positive tests/ No. performed	No of test-positive patients/ No. of patients tested
Specific IgE[a]	21/115 (7.3%)[f]	12/26 (13.6%)[g]	0/170 (0%)[f]	0/62 (0%)[g]
Histamine release[b]	8/189 (2.4%)	4/39 (4.5%)	2/141 (0.6%)	2/49 (2.2%)
Patch test[c]	13/281 (1.7%)	7/26 (8.0%)	0/456 (0%)	0/61 (0%)
Skin prick test	0/173 (0%)	0/34 (0%)	0/300 (0%)	0/85 (0%)
Intradermal test[d]	64/225 (15.9%)	24/37 (25.8%)	0/176 (0%)	0/56 (0%)
Drug challenge test[e]	46/116 (11.3%)	33/44 (25.9%)	0/188 (0%)	0/83 (0%)

[a]Grass: 6 (6 patients), insulins: 10 (4 patients), penicillins: 5 (2 patients).
[b]Ibuprofen: 2 (2 patients), insulins: 4 (2 patients), β-lactams[c]: 3 (1 patient), protamine: 1 (1 patient). 2 tests dismissed as false positive (1 ibuprofen and 1 dicloxacillin) due to lack of correlation with skin tests and DCT.
[c]ASA: 1 (1 patient), β-lactams (Penicillin G, penicillin V, ampicillin, amoxicillin, dicloxacillin, cefuroxime): 9 (3 patients), lidocaine: 1 (1 patient), phenylephrine: 2 (2 patients).
[d]β-lactams[c]: 7 (5 patients), excipients (metacresol, protamine.): 12 (6 patients), heparins: 4 (1 patient), insulins: 39 (10 patients), phenylephrine: 1 (1 patient), steroids: 1 (1 patient) 1 doubtful reaction to Engerix B®.
[e]ASA: 3 (3 patients), allopurinol: 2 (2 patients), β-lactams: 10 (7 patients), ceterizine: 1 (1 patient), ciprofloxacine: 1 (1 patient), diclofenac: 2 (2 patients), extracts for desensitisation 12 (12 patients), excipients: 4 (1 patient), ibubrufen: 1 (1 patient with negative DCT to ASA), insulins: 9 (2 patients), Ampicillin or gentamycin: 1 (1 patient).
[f]% of positive tests in relation to the skin of patients (CADR and non-CADR).
[g]% of test-positive patients with CADR and non-CADR.

and the percentage of positive tests of the total number performed, as well as the culprits identified with the individual tests are listed. The number of positive individual tests as well as the results for the test positive patients is given for patients both with and without CADR.

DISCUSSION

The prevalence of CADR in a university hospital department of dermatology found in this study was 1.35%. The pattern of reactions and eliciting drug groups was different from previous reports of the epidemiology of CADR in the literature, and different from the pattern we have published for a hospital population with in- and out-patients in the same institution (5). A high rate of local reactions and reactions from insulins and extracts for desensitization to grass was found, the latter in accordance with results from other allergy clinics in Denmark in the last couple of years, and reflects the referral traditions to the Allergy Centre when immediate type reactions are suspected. From the data presented here, the occurrence of atopy and contact allergy in patients with CADR does not seem to be increased compared with the normal population.

Figure 1 illustrates the distribution of the imputability scores. In the Dermatology Clinic as opposed to the Allergy Centre a large part of the patients scored "possible", and did not qualify for CADR. An explanation for this, and a possible source of bias, is that the Allergy Centre traditionally investigates patients with immediate reactions, where diagnostic tools for determining exact drug imputability are available, whereas delayed type reactions where the only diagnostic tool may be the history, are traditionally seen in the dermatology clinic.

The value of the diagnostic tests employed in this study is questionable since there is no generally accepted gold standard, and since the outcome of the tests are used diagnostically. Eosinophilia in peripheral blood or tissue has been associated with CADR in 36–75% of cases (12, 13). Romagosa et al. (12) found tissue eosinophilia in 24% of patients with CADR; only half of these had peripheral eosinophilia. S-tryptase has been shown to demonstrate activation of mast cells in patients experiencing immediate allergic reactions (14), but is not specific to immunological mast cell activation (15). Furthermore, evaluating the value of specific diagnostic tests should not be attempted unless all patients have been tested with the tests in question.

In the majority of drug allergic reactions the determinant is not known, but may represent a metabolite of the drug. Furthermore, the IgE response in the individual patient may be heterogeneous with IgE towards one or several different epitopes, as demonstrated in patients allergic to penicillin (16, 17). This may explain the low sensitivity and negative predictive value of RAST in penicillin allergy, and the lack of positive tests for specific IgE in the present study. In agreement with previous findings (5, 18), HR was of little value in the diagnosis of drug allergy; only 6.8% tested positive and 2/6 were false positive.

Barbaud et al. (19), found 72% of their ACDR patients having a positive skin test: 43%, 24%, and 67% in patch test SPT, and IDT, respectively. Correspondingly, we diagnosed 44.2% by skin tests: 10% by patch test, 0% by, SPT and 34.2% by IDT. However, testing in this selected group of patients yielded more positive tests than reported for a hospital population with acute cutaneous drug reactions (5). The differences can be explained by differences in test strategy.

DCT was done according to protocol in 31.6%. This is in agreement with our previous findings, where DCT was necessary to diagnose 5 of 15 penicillin allergic patients with negative specific IgE (20), and with the conclusions of international guidelines (9, 21).

Two patients had positive reactions in DCT with an NSAID, but not to ASA, indicating mechanism other than ASA intolerance. As previously reported (22) a case of bullous pemphigoid caused by penicillin had positive specific IgE, HR, and patch tests to penicillins.

Approximately half of the patients primarily seen in the dermatology clinic were not skin tested, compared with all patients seen in the Allergy Centre. This may have biased the results in the direction of a lower prevalence, and a relative over-representation of immediate type reactions. However, patients suffering from drug-induced dermatological diseases, such as subacute cutaneous lupus erythematosus or bullous pemphigoid, may show positive patch tests to the offending drug, even though the relevance of the reactions may be questionable (22, 23).

The reactions to grass pollen desensitization extracts reflected an "epidemic" seen in Denmark during the study period. Although extensive investigations were initiated both by the manufacturer and by the Danish Drug Agency, no explanation to the reactions seen hours after injection were found. The acute reaction to the extracts was, on the other hand, explainable and expected.

Retrospective investigations of drug allergies/drug eruptions have several weaknesses: Data are frequently lacking, definition of terms may be vague, registration may be incomplete, and the "gold standard" of diagnosis – the imputability analysis – may be subject to inter-observer variation. Nevertheless, investigations such as the present one suggest the extent and character of the problem, and may contribute to improvements in diagnostic procedures and guidelines.

REFERENCES

1. Gardner P, Cluff LE. The epidemiology of adverse drug reactions. A review and perspective. Johns Hopkins Med J 1970; 126: 77–87.
2. Hallas J, Gram LF, Grodum E, Damsbo N, Brosen K, Haghfelt T, et al. Drug related admissions to medical wards: a population based survey. Br J Clin Pharmacol 1992; 33: 61–68.
3. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001; 357: 1851–1853.
4. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003; 149: 1018–1022.
5. Borch JE, Andersen KE, Bindslev-Jensen C. Prevalence of acute cutaneous drug reactions in a university hospital. Acta Derm Venereol, in press.
6. Moore N, Biour M, Paux G, Loupi E, Begaud B, Boismare F, et al. Adverse drug reaction monitoring: doing it the French way. Lancet 1985; 2: 1056–1058.
7. Skov PS, Mosbech H, Norn S, Weeke B. Sensitive glass microfibre-based histamine analysis for allergy testing in washed blood cells. Results compared with conventional leukocyte histamine release assay. Allergy 1985; 40: 213–218.
8. EAACI. Position paper: allergen standardization and skin tests. Report No. 48 suppl. Copenhagen: Munksgaard, 1993.
9. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58: 854–863.
10. Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 2001; 45: 321–328.
11. Wahlberg JE, Lindberg M. Patch testing. In: Frosch PJ, Menne T, Lepoittevin J-P, eds. Textbook of contact dermatitis, 4th edn. Berlin: Springer Verlag, 2006: p. 365–390.
12. Romagosa R, Kapoor S, Sanders J, Berman B. Inpatient adverse cutaneous drug eruptions and eosinophilia. Arch Dermatol 2001; 137: 511–512.
13. Neukomm CB, Yawalkar N, Helbling A, Pichler WJ. T-cell reactions to drugs in distinct clinical manifestations of drug allergy. J Investig Allergol Clin Immunol 2001; 11: 275–284.
14. Ordoqui E, Zubeldia JM, Aranzabal A, Rubio M, Herrero T, Tornero P, et al. Serum tryptase levels in adverse drug reactions. Allergy 1997; 52: 1102–1105.
15. Veien M, Szlam F, Holden JT, Yamaguchi K, Denson DD, Levy JH. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. Anesthesiology 2000; 92: 1074–1081.
16. Zhao Z, Baldo BA, Baumgart KW, Mallon DF. Fine structural recognition specificities of IgE antibodies distinguishing amoxicilloyl and amoxicillanyl determinants in allergic subjects. J Mol Recognit 2001; 14: 300–307.
17. Moreno F, Blanca M, Mayorga C, Terrados S, Moya M, Perez E, et al. Studies of the specificities of IgE antibodies found in sera from subjects with allergic reactions to penicillins. Int Arch Allergy Immunol 1995; 108: 74–81.
18. Demoly P, Lebel B, Messaad D, Sahla H, Rongier M, Daures JP, et al. Predictive capacity of histamine release for the diagnosis of drug allergy. Allergy 1999; 54: 500–506.
19. Barbaud A, Reichert-Penetrat S, Trechot P, Jacquin-Petit MA, Ehlinger A, Noirez V, et al. The use of skin testing in the investigation of cutaneous adverse drug reactions. Br J Dermatol 1998; 139: 49–58.
20. Borch JE, Bindslev-Jensen C. Udredning af penicillinallergi. Procedurer og retrospektiv opgørelse af resultater for perioden 1997-2001. [Investigation of penicillin allergy. Procedures and retrospective statement of results for the period 1997 to 2001]. Ugeskr Laeger 2003; 165: 3157–3161.
21. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy 2003; 58: 961–972.
22. Borch JE, Andersen KE, Clemmensen O, Bindslev-Jensen C. Drug induced bullous pemphigoid with positive patch-test and in vitro IgE-sensitization. Acta Derm Venereol 2005; 85: 171–172.
23. Deleuran M, Clemmensen O, Andersen KE. Contact lupus erythematosus. Contact Dermatitis 2000; 43: 169–170.
24. Borch JE, Bindslev-Jensen C. Delayed-type hypersensitivity to heparins. Allergy 2004; 59: 118–119.