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ORIGINAL ARTICLE

Drug allergy in tertiary care in Turkey: Results of a national survey. The ADAPT study: Adult drug allergy perception in Turkey

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Abstract
Background: No data are available on the incidence of drug hypersensitivity (DH) reactions in outpatient settings of tertiary allergy/immunology clinics. Our aims were to document the frequency of outpatient hospital admissions due to DH reactions to allergy/immunology clinics in adults and the management of these reactions in real life. We also investigated whether drug allergy affected social and medical behaviours of the patients.
Methods: This multi-centre study was performed for one year with the participation of 11 out of 16 tertiary allergy/clinical immunology clinics in Turkey. The study group consisted of the patients with DH reactions. Results of a questionnaire including drug reactions and management were recorded.
Results: Among 54,863 patients, 1000 patients with DH were enrolled with a median of 2.1% of all admissions. In real life conditions, the majority of approaches were performed for finding safe alternatives (65.5%; 1102 out of 1683) with 11.7% positivity. Diagnostic procedures were

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positive in 27% (154/581) of the patients. The majority of the patients had higher VAS scores for anxiety. A total of 250 subjects (25%) reported that they delayed some medical procedures because of DH.
Conclusion: Our results documented the frequency of admissions due to DH reactions to allergy/clinical immunology clinics for the first time. Although physicians mostly preferred to perform drug tests in order to find safe alternatives, considering the fact that DH was confirmed in 27% of the patients, use of diagnostic tests should be encouraged, if no contraindication exists in order to avoid mislabelling patients as DH.

Introduction

Adverse drug reactions [ADRs] have been shown to cause significant morbidity in hospitalised patients, with an increment in the hospital cost.[1–4] Most of our knowledge about ADRs has come from studies performed on hospitalised patients.[1–6] These reactions are mainly based on retrospective evaluation of hospital data in which not only drug hypersensitivity reactions but also all ADRs are included.[5–8] The burden of drug hypersensitivity is based mostly on self-reported data, in which variation in the prevalence rates of drug allergy/hypersensitivity in adults was shown, dependent on the discrepancies in methodology and study populations.[9–13] On the other hand, very limited data are available on the incidence of drug reactions in outpatient clinical settings.[14] In Turkey, a few population-based studies in some selected groups have provided prevalence rates of self-reported drug hypersensitivity reactions of 2.9%[15] and 4.7%[16] in two separate studies performed among medical students, and of 3.6%[17] in male adults.

Drug allergy/hypersensitivity reactions are one of the most challenging areas for the allergists/clinical immunologist in their daily lives. Besides self admissions by the patients, these patients are also referred to allergists/immunologists by primary care physicians as management of drug allergy/hypersensitivity reactions are complex for a primary care physician. Management of these cases is mainly based on recommendations of international guidelines and requires a careful approach to the patients' history, as well as performing drug skin testing and provocation tests mainly based on the need of the patients.[18–22] These tests are mainly used for finding safe alternatives or to establish true diagnosis of drug hypersensitivity. However, so far, no data exist on hospital admissions due to drug hypersensitivity reactions to allergy/clinical immunology centres. In addition, it is also not reported how these tests are translated into real life.

Therefore, the primary aim of this multi-centre study was to assess the frequency of outpatient hospital admissions to tertiary allergy/immunology clinics due to drug allergy/hypersensitivity in an adult population of Turkey. Secondarily, we aimed to document clinical practice in the management of drug allergy in real-life conditions. We also hypothesized that drug allergy might affect some social and medical behaviours of the patients, and this hypothesis was investigated as a secondary aim of this study.

Materials and methods

Study settings

This is a multi-centre study that was performed prospectively for one year between 2009 and 2010. Candidate study centres were tertiary care allergy/clinical immunology clinics of Turkey. In 2009, there were 16 tertiary care clinics including university hospitals and training and research state hospitals in the field of allergy/clinical immunology serving adult patients in Turkey. Initially, all centres were invited to take part in the study, of which, 11 centres agreed to participate. Study centres were in the Central Anatolia Region [Ankara University; Atatürk Training and Research Hospital of Surgery and Diseases of the Chest; Cumhuriyet University; Fatih University; Hacettepe University; Kırıkkale University; Gaziosmanpaşa University], the Marmara Region (Northwest part of Turkey) [Istanbul University], and the Aegean Region (West Coast of Turkey) [Celal Bayar University; Ege University; Izmir Atatürk Research and Training Hospital].

Study group

All the cases who were admitted to the outpatient clinics of the study centres were screened for drug allergy/hypersensitivity reactions. The reactions considered to be related to drug hypersensitivity were immediate reactions (urticaria/angio-oedema, bronchospasm, laryngeal oedema, rhinitis, and systemic anaphylactoid reactions involving hypotension, laryngeal oedema, bronchospasm and/or shock) and non-immediate reactions (maculopapular eruption, fixed drug eruption, photosensitivity, contact dermatitis, and other reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) to a prescribed drug. The patients who described a reliable history of one of these reactions related to any drug use were enrolled in the study. A detailed questionnaire including current and past history related to drug reactions as well as physical examination were performed in each patient by an allergist/immunologist. In the history, reaction pattern, timing of the reaction after drug use, any similar reaction in the past, any improvement after drug removal, and presence of any individual risk factors, etc. were questioned in detail. At the end of one year, all centres documented their annual outpatient clinic number in order to calculate the frequency of drug allergy/hypersensitivity-related hospital admission

among all allergy admissions. The study was approved by the ethics committee.

Study protocol

A detailed documentation related to drug hypersensitivity reactions, risk factors, and the procedures performed on the patients were recorded for this study.

Part I: Demographics and disease characteristics such as age, gender, presence of co-morbid conditions, and family history of drug hypersensitivity.
Part II: Characteristics of drug hypersensitivity reactions [type of reaction, duration, culprit drug(s), and number of reactions].
Part III: The management of the patients in terms of procedures performed on the patients and the outcomes of these tests [see below].
Part IV: This part included assessment of the attitude of the patients towards any drug use, anxiety level, and factors related to anxiety. Anxiety was determined by visual analogue scale (VAS). In this analysis, ''0'' indicated no anxiety related to drug hypersensitivity, whereas ''10'' indicated the highest anxiety level related to drug hypersensitivity. The other items evaluated in this part of the study were related to whether the patients exhibited any limitations in their daily life due to drug hypersensitivity. Finally, the patients were also asked whether they had any limitation in medical procedures because of drug hypersensitivity. The items included in this part were derived from a previous focus-group discussion performed by a significant number of patients seen at Ankara University allergy outpatient clinic.

Management of the patients

No specific attempts related to this study were conducted; instead, usual management was provided by each physician specifically based on the history and the need of the patients. Recommendations of the European Network for Drug Allergy (ENDA) were followed for management of drug hypersensitivity reactions.[18–22]

Following the initial assessment, the patients were tested for diagnostic purposes and/or for finding safe alternatives depending on the history and their individual needs. All drug tests were performed under strict medical surveillance in a hospital setting. For diagnostic approach, skin tests were performed initially if a skin testing material was available. Skin prick and intradermal tests were used for the diagnosis of IgE-mediated drug reactions, such as urticaria, angio-oedema, anaphylaxis, dyspnoea, and rhinitis,[20,21] whereas patch tests and delayed reading of intradermal tests were performed for the diagnosis of non-immediate reactions.[22] If these tests were negative, drug provocation tests (DPTs) were performed.[18] Briefly, drug tests were not performed in cases who had the reaction within the previous 4–6 weeks; used a medication that could affect the test outcome, such as antihistamines and oral steroids; had active signs of underlying disease such as urticaria, uncontrolled asthma (forced expiratory volume in 1 second [FEV_1] value <70% of predicted); uncontrolled cardiac, renal or hepatic disease; as well as current upper airway infection. DPTs were not performed in the patients who experienced severe reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, drug-induced hypersensitivity reactions, acute generalised exanthematous pustulosis, as well as manifestations of specific organ involvement.[18]

Drug provocation tests were also performed to find safe alternatives.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v.11.0; Chicago, IL, USA) for Windows. Numeric values were expressed as mean ± SEM, whereas nominal values were given as *n* (%). Chi-square tests were used for comparison of nominal values. Assessment of factors related to severe reactions and anxiety level were performed by univariate analysis. The factors in the multivariate analysis were age, gender, duration of drug allergy, presence of asthma, chronic urticaria, previous reactions, and culprit drugs. All directional *p* values were two-tailed, and significance was assigned to values lower than 0.05.

Results

Study group

Among 54,863 patients screened for drug hypersensitivity, 1000 had a history of drug hypersensitivity, leading to an admission rate of between 0.01 and 4.3% (median 2.1%).

Part I: Demographics and characteristics of the group

Females predominated in the study group (76.7%) [Table 1]. Asthma, psychiatric disorders and chronic urticaria were the most common co-morbid disorders [Table 1].

Part II: Characteristics of the drug hypersensitivity

Non-steroidal anti-inflammatory drugs (NSAIDs) were the most common cause of hypersensitivity reactions, followed by beta-lactam antibiotics [*n*: 612, 61.1% and 347, 34.7%, respectively] [Table 2]. The most common clinical presentations involved the skin. The frequency of urticaria with or without angio-oedema was 54.7%.

Part III: Management of the patients

Considering the procedures performed for the management of drug hypersensitivity, a total of 1683 approaches were performed, 581 (34.5%) of which served for diagnostic purpose and 1102 (65.5%) for finding safe alternatives [Table 3]. Among 581 diagnostic procedures, 154 (27%) were positive. A total of 1102 drug challenges for finding safe alternatives were performed. One hundred and thirty provocations (11.7%) were positive [Table 3].

Table 1 Demographics and disease characteristics of the patients.

Variable	
n	1000
Gender (female) n (%)	765 (76.7%)
Age distribution n (%)	
18–35 years	363 (36.3%)
36–50 years	378 (37.8%)
51–65 years	204 (20.4%)
66–80 years	29 (2.7%)
Occupation n (%)	
Housewife	381 (38.1%)
Clerk	127 (12.7%)
Student	55 (5.5%)
Others	80 (8%)
Co-morbid disorders	
Asthma	264 (26.4%)
Chronic urticaria	101 (10.1%)
Psychiatric disorders	111 (11.1%)
Chronic sinusitis	84 (8.4%)
Nasal polyps	75 (7.5%)
History of drug allergy in family members	97 (9.7%)

Table 2 Characteristics of hospital admission and history of drug hypersensitivity.

Variable	
Referral by a physician n (%)	233 (23.3%)
Admission due to primarily drug reactions n (%)	960 (96%)
Prior history of admission to a physician because of drug hypersensitivity	651 (65%)
Number of drug reactions (mean ± SEM)	2.3 ± 0.04
Age at first drug reaction (mean ± SEM) (years)	33.2 ± 0.47
Time since the first drug reaction (mean ± SEM) (months)	84.01 ± 3.4
Single reactors n (%)	662 (69.2%)
Multiple reactors n (%)	294 (30.8%)
Drugs causing reactions n (%)	
NSAIDs	612 (61.1%)
Beta-lactam antibiotics	347 (34.7%)
Non beta lactam antibiotics	131 (13.1%)
Local anaesthetics	51 (5.1%)
Neuromuscular blocking agents	11 (1.1%)
Hypersensitivity reactions caused by drugs n (%)	
Cutaneous	520 (54.7%)
At least two system involvement	200 (21%)
Respiratory	94 (9.8)
Anaphylactic shock	47 (4.9%)
Maculopapular eruption	25 (2.6%)
Fixed drug eruption	18 (1.9%)
Other cutaneous reactions	11 (1.25)

Table 3 Result of drug tests.

Variable	
Number of diagnostic tests	**581**
# of positive tests n (%)	154 (27%)
Positivity by skin prick/intradermal tests n (%)	58 (37.6%)
Positivity by drug provocation tests n (%)	96 (62.3%)
Positivity according to culprit drugs n (%)	
Analgesics	71/224 (31.9%)
Beta-lactam antibiotics	39/191 (20.4%)
Non beta-lactam antibiotics	
Quinolones	10/19 (52.6%)
Macrolides	3/14 (21.4%)
Other non beta-lactam antibiotics	0/8 (0%)
Neuromuscular blocking agents	4/12 (25%)
Local anaesthetics	8/43 (18.6%)
Number of tests for finding safe alternatives	**1102**
Number of positive tests n (%)	130 (11.7%)
Positivity according to alternative drugs n (%)	
NSAIDs	
Nimesulide	18/104 (17.3%)
Meloxicam	6/130 (4.6%)
Paracetamol	5/76 (6.5%)
Non beta-lactam antibiotics	
Quinolones	26/117 (22.2%)
Macrolides	10/115 (8.7%)
Beta lactam antibiotics	20/116 (17.2%)
Local anaesthetics	4/47 (8.5%)
Neuromuscular blocking agents	6/36 (16.6%)

Part IV: Social and medical impact of drug allergy

Considering the attitudes towards drug use of the patients with a history of drug hypersensitivity, 180 (22.8%) reported avoiding not only the use of the culprit drug but also other drugs. The majority of the patients (*n*: 485; 60.9%) preferred to use paracetamol as an analgesic. According to VAS, the majority had higher anxiety scores [Fig. 1]. The main reason for this anxiety was the fear of recurrence of the previous reactions (*n*: 318; 69.6%), fear of death (*n*: 69, 15.1%), and fear of permanent impairment in the body (*n*: 27; 5.9%).

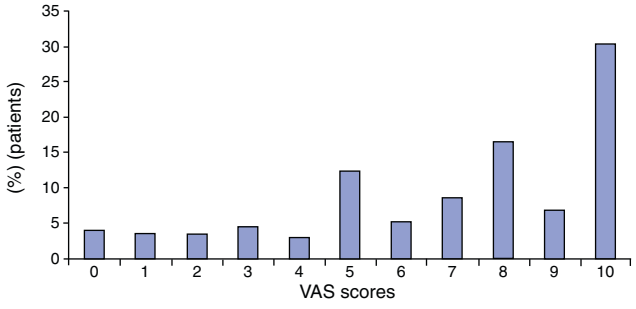

Figure 1 Anxiety level of the patients because of drug reactions (VAS scores).

Table 4 Limitations of the patients in daily life and medical procedures.

	n (%)
Social activities	
Exercise (including jogging, walking)	188 (23.8%)
In-house activities (cleaning, cooking, etc.)	163 (20.6%)
Participating in social activities	79 (10%)
Watching television	61 (7.7%)
Cognitive activities (reading book, newspaper, studying, homework)	56 (7.1%)
Daily work activities	54 (6.8%)
Medical activities	
Avoidance of diagnostic procedures with contrast media	28 (3.5%)
Delay in elective surgery	74 (9.3%)
Dental manipulations without any medications	65 (8.2%)

Presence of depression was the only factor correlated with higher anxiety scores ($p < 0.001$).

Some of the patients reported limitations in their daily life because of drug allergy [Table 4]. Drug hypersensitivity caused some limitations in medical procedures as well. A total of 250 subjects (25%) reported that they delayed some medical procedures [Table 4].

Discussion

This nationwide multi-centred study showed that admission to adult outpatient allergy/immunology clinics of tertiary care hospitals in Turkey due to drug hypersensitivity was around 2% of all admissions. In practical life, allergists mostly preferred to perform drug testing in order to find safe alternatives. On the other hand, based on the diagnostic test results, only a minority of the subjects had true drug hypersensitivity. Our results also showed that having a drug hypersensitivity might cause anxiety in the patients, which eventually leads to limitations in some social behaviour such as reading books, watching television or joining a social environment to avoid extra drugs such as pain killer use. Some patients also demonstrated similar avoidance behaviour in some medical procedures in which medication use was necessary.

As an outstanding finding in our study, we showed that around 2% of the outpatient clinic admissions to tertiary care clinics of allergy/immunology in Turkey were due to reactions related to drug hypersensitivities. Admission rates varied between 0.08 and 4.6% of all admissions among study centres mainly depending on referral rate, city, and population of the city. In this study, all the cases admitted to the study centres were evaluated by an allergist/immunologist and other types of drug reactions were not included, in order to show the true frequency of admissions due to drug hypersensitivity reactions. Previous studies performed in outpatient groups involved the cases with either cutaneous findings or all adverse effects without making a definitive conclusion on data related to allergic or hypersensitivity drug reactions.[5–8] Therefore, we believe our result makes a significant contribution to the current literature by providing data on admissions due to drug hypersensitivity reactions to allergy/immunology clinics for the first time.

We also showed that our results reflect the nationwide incidence of drug hypersensitivity reactions among patients who admitted to tertiary allergy/immunology outpatient clinics in Turkey, as the majority of the tertiary care clinics in the country participated in the study. On the other hand, although this data provided information about the frequency and characteristics of the hospital admissions related to drug hypersensitivity reactions to tertiary care clinics in our country, these results may not reflect the patient profile in primary care.

Characteristics of the reactions and the culprit drugs were in accordance with previous trials.[9–17] The majority of the reactions were immediate-type drug reactions and mainly involved the skin. Non-immediate reactions were relatively less common. Compatible with the previous epidemiological studies, NSAIDs and beta-lactam antibiotics were the most common culprit drugs causing hypersensitivity reactions in the current study.[9–17]

Our results also showed how recommendations of international guidelines on drug hypersensitivity reactions were followed in real life conditions. In this study, no specific attempts related to this study were conducted; instead physicians followed the international guidelines and made their decisions depending on the conditions and patients' needs. In this sense, the allergists mostly preferred to perform drug tests to find safe alternatives. Diagnostic approaches were applied less frequently. Although primarily not investigated in this study, the main reasons for choosing to test for finding safe alternatives could be physicians' preference, mainly based on the relatively safe profile of these tests in comparison to those done for diagnostic purposes, inappropriate conditions for diagnostic testing (timing, presence of active reactions, taking medicine by the patients, etc.), concerns raised by the patients, presence of no data about the name of the culprit drug and experience of the physicians on drug tests.

Another important outcome of this study was provided from diagnostic test results. Previous studies showed that history alone was not sufficient for labelling the patients as drug allergic.[23–26] Messaad et al. showed that among 1372 drug provocations, only 241 (17.6%) were positive.[23] A study from Korea included children with suspicion of drug allergy, and 17 out of 71 drug provocation tests were positive.[24] In Brazil, 243 DPTs were performed in 198 patients and only 10 (4%) were positive.[25] Another study from Finland also suggested similar results.[26] Despite slightly higher positivity in diagnostic drug tests compared to those previous trials, our result also supported low diagnostic accuracy in drug hypersensitivity reactions with 27% positivity in diagnostic procedures. All this current and past data emphasize the importance of performing diagnostic tests by allergists, if there is no contraindication for these tests. This approach allows to exclude mislabelling the patients as drug-allergic, and thereby prevents using more toxic and expensive drugs in these cases in the future.

A significant number of drug testings were performed in order to find safe alternatives. The majority of the patients with cross-reactive NSAIDs hypersensitivity were tested by Meloxicam and Nimesulide, currently available NSAIDs in

Turkey that preferentially inhibit cyclo-oxygenase-2 (COX-2), and these drugs were found to be generally well tolerated in the majority of the patients (tolerability rates Nimesulide: 82.7% and Meloxicam: 95.7%), in accordance with previous trials.[27–31] Macrolide antibiotics were the most common tested drug for finding a safe antimicrobial drug, assuming their extended spectrum and safe profile. However, the fact that there are cases that reacted to the alternative drugs suggests, once again, that these drugs should be tested for tolerability before prescribing them.

Importantly, none of the patients in this series who had been challenged for either the diagnostic aim or for finding safe alternatives showed fatal or life-threatening severe reactions. All of the cases in this study were strictly evaluated not only for indications but also for contraindications of the drug tests as stated in the guidelines. Thus, our results suggest that if the recommendation of ENDA and other guidelines are strictly followed, performance of these tests does not lead to undesired outcomes in terms of safety.

In this study, we also investigated whether having drug hypersensitivity caused any anxiety in the patients. Interestingly, we noticed that the majority of the patients had a high anxiety level based on VAS scores. Fears about recurrence of the previous reactions and of death were the main causes of this anxiety. Having a diagnosis of chronic depression was the only factor that was related to anxiety of the patients. However, as a limitation of this study, anxiety level was assessed by VAS score, and no test specific to anxiety was performed, as this study was performed as a part of daily routine. Previous studies showed that somatisation, anxiety and depression were part of the symptoms in patients with drug intolerance[32] and multiple-drug allergy syndrome.[33] Thus, physicians who deal with patients having drug hypersensitivity should be aware of a possible higher anxiety level in patients with drug hypersensitivity and chronic depression and should take the necessary actions.

Our study also documented that some social and medical behaviours of the patients with drug hypersensitivity were influenced. It is worth noting that there were patients who avoided some social activities such as reading books and joining friends' groups. This kind of avoidance behaviours are mainly due to preventing extra use of some drugs such as analgesics as these activities can lead to headaches that might require analgesics. These cases also avoided some medical interventions that required medication use. The main reason for this avoidance was to prevent drug use in order to protect themselves from further drug reactions. Of interest, approximately 1 in 5 patients reported not using any drug because of a drug allergy history. In fact, documentation of such limitations in our group highlights that the physicians should devote more time to the concerns of these patients and should discuss this issue with them.

In conclusion, our results documented the frequency of admissions due to drug hypersensitivity reactions to tertiary allergy/clinical immunology outpatient clinics for the first time. Our results also showed another aspect of drug hypersensitivity reactions by documenting the limitations of their social life as well as negative attitude towards further drug use and some medical procedures in a significant number of cases with drug hypersensitivity. Although physicians mostly preferred to perform drug tests in order to find safe alternatives, considering the fact that drug allergy/hypersensitivity was confirmed by drug tests in approximately 1 in 3 patients, use of diagnostic tests should be encouraged, if no contraindication exists, in order to avoid mislabelling patients as drug-hypersensitive and to prevent unnecessary limitations in their social and medical lives due to avoid extra drug use such as analgesics by the patients.

Ethical disclosures

Patients' data protection. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Protection of human subjects and animals in research. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Conflict of interest

The authors have no conflict of interest to declare.

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References

1. McDonnell PJ, Jacobs MR. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001;52:77–83.
2. Gomes ER, Demoly P. Utilization of hospital and outpatient care for adverse cutaneous reactions to medications. Pharmacoepidemiol Drug Saf. 2005;14:677–84.
3. Impicciatore P, Choonara I, Clarkson A. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother. 2000;34:1373–9.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279:1200–5.
5. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. Allergy. 1997;52:388–93.
6. Hernández-Salazar A, Rosales SP, Rangel-Frausto S, Criollo E, Archer-Dubon C, Orozco-Topete R. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. Arch Med Res. 2006;37:899–902.
7. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of acute cutaneous drug reactions in a Scandinavian university hospital. Acta Derm Venereol. 2006;86:518–22.

8. 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;149:1018–22.
9. Demoly P, Hillaire-Buys D. Classification and epidemiology of hypersensitivity drug reactions. Immunol Allergy Clin North Am. 2004;24:345–56.
10. Demoly P, Gomes ER. Drug hypersensitivities: definition, epidemiology and risk factors. Eur Ann Allergy Clin Immunol. 2005;37:202–6.
11. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309–16.
12. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34:1597–601.
13. Dorner T, Lawrence K, Rieder A, Kunze M. Epidemiology of allergies in Austria. Results of the first Austrian allergy report. Wien Med Wochenschr. 2007;157:235–42.
14. Ghandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. N Engl J Med. 2003;348:1556–64.
15. Kalyoncu AF, Karakoca Y, Demir AU, Alpar R, Shehu V, Çöplü L, et al. Prevalence of asthma and allergic diseases in Turkish university students in Ankara. Allergol Immunopathol (Madr). 1996;24:152–7.
16. Bavbek S, Erkekol FO, Celik GE, Gönüllü I, Mısırlıgil Z. Self-reported prevalence of hypersensitivity reactions against drugs among medical students: does awareness cause any difference. Pharmacoepidemiol Drug Saf. 2011;20:154–61.
17. Kurt E, Demir AU, Cadirci O. Immediate type drug hypersensitivity reactions and associated risk factors in an adult Turkish men population. Iran J Allergy Asthma Immunol. 2010;9:245–50.
18. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854–63.
19. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy. 2002;57:45–51.
20. Kränke B, Aberer W. Skin testing for IgE-mediated drug allergy. Immunol Allergy Clin North Am. 2009;29:503–16.
21. Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. Med Clin North Am. 2010;94:805–20.
22. Torres MJ, Mayorga C, Blanca M. Nonimmediate allergic reactions induced by drugs: pathogenesis and diagnostic tests. J Investig Allergol Clin Immunol. 2009;1:80–90.
23. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004;140:1001–6.
24. Na HR, Lee JM, Jung JW, Lee SY. Usefulness of drug provocation tests in children with a history of adverse drug reaction. Korean J Pediatr. 2011;54:304–9.
25. Aun MV, Bisaccioni C, Garro LS, Rodrigues AT, Tanno LK, Ensina LF, et al. Outcomes and safety of drug provocation tests. Allergy Asthma Proc. 2011;32:301–6.
26. Lammintausta K, Kortekangas-Savolainen O. Oral challenge in patients with suspected cutaneous adverse drug reactions: findings in 784 patients during a 25-year-period. Acta Derm Venereol. 2005;85:491–6.
27. Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. Ann Pharmacother. 2007;41:1191–200.
28. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. Treat Respir Med. 2006;5:399–406.
29. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA. Allergy. 2011;66:818–29.
30. Kalyoncu AF, Karakaya G, Bozkurt B, Artvinli M. A new method of oral drug provocation testing for determining safe alternatives for patients with non-steroidal anti-inflammatory drug intolerance: the triple test. Int Arch Allergy Immunol. 2005;138:319–23.
31. Çelik G, Erkekol FO, Aydın O, Demirel YS, Mısırlıgil Z. Are drug provocation tests still necessary to test safety of COX-2 inhibitors in patients with analgesic hypersensitivity? Allergol Immunpathol (Madr. 2013;41:181–8.
32. Hassel JC, Danner D, Hassel AJ. Psychosomatic or allergic symptoms? High levels for somatization in patients with drug intolerance. J Dermatol. 2011;38:959–65.
33. De Pasquale T, Nucera E, Boccascino R, Romeo P, Biagini G, Buonomo A, et al. Allergy and psychologic evaluations of patients with multiple drug intolerance syndrome. Intern Emerg Med. 2012;7:41–7.