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DERLEME REVIEW

Drug hypersensitivity: history taking and construction of a test plan

İlaç aşırı duyarlılığı: Öykü alınması ve test planı oluşturulması

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ABSTRACT

Drug hypersensitivity, including allergic reactions, is one of the side effects of drugs and is a daily worry for the clinician. They can be classified as immediate or non-immediate according to the time interval between last drug administration and onset. Immediate reactions occur within one hour and are manifested by urticaria, angioedema, bronchospasm, and anaphylactic shock. Non-immediate reactions occur after more than one hour and are manifested by maculopapular eruption, urticaria and serum sickness. Clinical and immunological studies suggest that type I (IgE-mediated) and type-IV (cell-mediated) pathogenic mechanisms are involved in most immediate and non-immediate reactions, respectively. New diagnostic tools, such as the basophil activation test and the lymphocyte activation test, have been developed and are under validation. When properly performed in specialised centres, a firm diagnosis is often possible and safe alternative medication can be proposed. In diagnosis, the patient's history is fundamental; the allergologic examination includes in vivo and in vitro tests selected on the basis of the clinical features. Determination of specific IgE levels is still the most common in vitro method for diagnosing immediate reactions. The clinical tools

ÖZET

Allerjik reaksiyonları da içeren ilaç duyarlılığı, ilaçların yan etkilerinden biridir ve klinisyen için günlük endişedir. Son ilaç uygulanması ve reaksiyonun ortaya çıkışı arasında geçen süreye göre erken ve geç ortaya çıkanlar olarak sınıflandırılır. Erken reaksiyonlar bir saat içinde oluşur ve ürtiker, anjiyoödem, bronkospazm ve anafilaktik şok ile belirti verir. Geç reaksiyonlar bir saatten daha sonra ortaya çıkar ve makülopapüler döküntü, ürtiker ve serum hastalığı ile belirti verir. Klinik ve immünolojik incelemeler erken reaksiyonlarda tip I (IgE aracılı), geç reaksiyonlarda ise tip IV (hücre aracılı) patogenetik mekanizmaların rol oynadığını düşündürmektedir. Bazofil aktivasyon testi ve lenfosit aktivasyon testi gibi yeni tanısal araçlar geliştirilmiş ve değerlendirilmektedir. Özelleşmiş merkezlerde düzgün yapıldığında kesin tanı çoğunlukla elde edilebilir ve güvenli alternatif ilaçlar önerilebilir. Tanıda, hastanın öyküsü vazgeçilmezdir; allergolojik inceleme, klinik özellikler temelinde seçilen in vivo ve in vitro testleri içerir. Erken reaksiyonların tanısında spesifik IgE düzeylerinin belirlenmesi hala en sık kullanılan in vitro yöntemdir. Kesin tanı sağlayan klinik araçlar sayıca azdır ve aşağıda yazılı işlemleri içerir: Ayrıntılı klinik öykü, standart deri testleri, güvenilir biyolojik testler ve ilaç provokasyon test-

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allowing a definite diagnosis are few in number and include the following procedures: a thorough clinical history, standardised skin tests, reliable biological tests and drug provocation tests. All of these tools, although not always validated or predictive at the individual level and sometimes dangerous, have been carefully evaluated by the European Network of Drug Allergy (the European Academy of Allergy and Clinical Immunology drug hypersensitivity group of interest).

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leri. Tüm bu araçların, kişi düzeyinde her zaman geçerli ve prediktif değere sahip olmamalarına ve bazen tehlikeli olabilmelerine karşın, Avrupa İlaç Allerjisi Ağı ("European Network of Drug Allergy-European Academy of Allergy and Clinical Immunology" ilaç hipersensitivite çalışma grubu) tarafından dikkatlice değerlendirilmiştir.

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Anahtar kelimeler: İlaç aşırı duyarlılığı, provokasyon testleri, hikaye

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INTRODUCTION

Drug hypersensitivity reactions may affect up to 20% of hospitalized patients and up to 7% of outpatients and can be life threatening[1]. A variety of reaction types have been described[1-3]. These include: (i) non-immunological reactions, (ii) IgE-mediated allergic reactions in the form of immediate anaphylactic shock, generalised urticaria, angioedema and/ or bronchospasm, (iii) non-immediate allergic reactions (which may occur several days after the last drug has been administered) such as urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms. Reactions occurring within a few hours following the last administration of the drug may due to IgE-dependent or non-immunological mechanisms. The former could be lethal. The latter occur in only a small percentage of patients and in general can not be predicted. The etiologies of these reactions include non-specific histamine release (e.g. opiates, radiocontrast media and vancomycin), bradykinin accumulation (angiotensin-converting enzyme inhibitors), complement activation (radiocontrast media and protamine), induction of leukotriene synthesis (non-steroidal antiinflammatory drugs) and bronchospasm (e.g. SO_2 released by drug preparations containing sulphites). Moreover, some reactions such as urticaria could even be not related to the drug itself, but to the underlying (e.g. infectious) disease.

Anaphylactic shock is one of the severe reactions commonly associated with drug allergy fatalities. It is usually an IgE-mediated reaction and it is the most frightening and potentially lethal allergic event. Non-IgE-mediated anaphylactic shocks can also be drug related and equally dangerous. Antibiotics take the first position. In the United Kingdom, where hospital admissions for acute anaphylaxis are increasing (from 56 per million in 1991 to 102 per million in 1995), the work by Pumphrey on deaths from anaphylaxis (1992-2001) shows that drugs are the leading cause (88 deaths out of 202) followed by food and insect stings[4,5]. Drug intake expose to drug sensitization and demonstrating drug allergy is mandatory to avoid relapses.

Therefore, a complete drug allergy work up is required, which includes a detailed clinical history and physical examination, followed by one or more of the following procedures: skin tests, laboratory tests and ultimately, drug provocation tests. Under the aegis of the European Academy of Allergy and Clinical Immunology, the European Network on Drug Allergy (ENDA) has been working for the establishment of clinical tools for the daily practice[6-13].

Clinical History

Clinical history should be extremely thorough and address the symptomatology (compatible with an allergy), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment), other medication taken (both at the time of the reaction and other drugs of the same class taken since), and the medical background of the patient (any suggestion of previous allergies whether associated with medications or not)[14]. Data should be taken in a uniform format and to harmonize our drug hypersensitivity diagnostic procedures in Europe, members of ENDA have first developed a questionnaire, available into many different languages[6]. It also includes some procedures as skin tests, provocation tests and biological tests.

The history is in fact often not reliable since different drugs are often taken simultaneously and can account for the symptoms, it is often unprecise[15]. Finally, the clinical picture of drug allergy is very heterogeneous, mirroring many distinct pathophysiological events. Anaphylaxis may be the easiest form to recognize. Thus, many doctors rely on history and some reference manuals for drug allergy diagnosis, without attempting to prove the relationship between drug intake and symptoms or to clarify the underlying pathomechanism of the reaction. Such an attitude leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field. In cases where an hypersensitivity reaction is suspected, if the drug is essential and/or frequently prescribed (e.g. beta-lactams, paracetamol and non-steroidal antiinflammatory drugs) a certified diagnosis should be performed and tests carried out in a specialist centre. Only a formal diagnosis of drug hypersensitivity reactions allows one to bring into play the measures required for prevention and treatment. For these drugs, the prudent principle of eviction may be insufficient. It would mean elimination of drugs which do not necessarily give rise to reactions and which are widely used. However, it is a valid option until a specialist consultation can be scheduled.

Skin Tests

The diagnostic value of skin tests has not been fully evaluated and the experience in different centres has rarely been exchanged during the last decades. Thus, reliable skin test procedures for the diagnosis of drug hypersensitivity are generally missing and test concentrations are unknown or poorly validated for most drugs. Skin tests have to be applied according to the suspected pathomechanism of the hypersensitive drug reactions. For immediate beta-lactam hypersensitivity reactions for example, an IgE-mediated mechanism can be demonstrated by a positive skin prick and/or intradermal test after 20 minutes[7,9].

Therefore, skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism and check for cross-reactivities[3,9,16]. They should be performed 4 to 6 weeks after the reaction, in a specialist environment, since the tests themselves can induce, although in rare cases only, an anaphylactic reaction[9]. Their sensitivity and predictive value vary depending on the drug from excellent (penicillins, myorelaxants, heterologous sera, enzymes) through satisfactory (vaccines, hormones, protamine, opiates, thiopental) and poor or unknown (local anesthetics, paracetamol, sulfonamides, iodine radiocontrast media, quinolones, non-steroidal antiinflammatory drugs, cephalosporins and other antiinfectious agents).

Provocation Tests

A drug provocation test is carried out for diagnostic/therapeutic purposes and consists of the controlled administering of the drug to a patient with a history suggesting a drug allergy. This drug is either an alternative, a structurally/pharmacologically related drug or the suspected drug itself. Although there are some criticism, the European Network for Drug Al-

lergy from the European Academy of Allergology and Clinical Immunology recommends their use to confirm drug hypersensitivity reactions when skin tests and biological tests are not available or not validated[8]. However, with the exception of some drugs such as aspirin, cyclooxygenase-2 inhibitors and beta-lactams, there exist only data on small cohorts reporting the results of drug provocation tests[17-19]. To demonstrate the outcome of drug provocation tests in the evaluation of patients with a history suggesting drug anaphylaxis, we have carried out 1372 drug provocations using a variety of drugs, including beta-lactams, aspirin and other non-steroidal antiinflammatory drugs, paracetamol, macrolides and quinolones[20]. The major result of this study is that a true drug hypersensitivity was represented in less than one quarter of the patients (17.6%). This was of crucial importance for the therapeutic future of these patients. It was found that non-hypersensitive patients did not need to avoid these drugs in the future. The continuous search for alternatives leads to fear and often only less potent alternatives are found. Drug provocation tests reproduced the same symptoms, albeit milder and of a shorter duration. Prednisolone, H1-antihistamines and epinephrine in cases of hypotension were administered, allowing a rapid and complete clearing of the reaction. Drug provocation tests should nevertheless be regarded as a serious and potentially dangerous procedure[9]. It is important to document the patient's personal details, medical history and concomitant drug therapy and to have full resuscitation facilities available during the tests.

CONCLUSION

The diagnosis of immediate drug hypersensitivity reactions is often difficult. It remains largely clinical. Skin tests are validated for some drugs. Provocation tests have the best sensitivity, are combersome and may be harmful. Better care for these patients, available to all clinicians, requires new and validated biological tools for diagnosis.

REFERENCES

1. *Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol 2005; 5:309-16.*
2. *Johansson S, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004; 113:832-6.*
3. *Gruchalla RS. Clinical assessment of drug-induced disease. Lancet 2000;356:1505-11.*
4. *Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. Br Med J 2000;320: 1441.*
5. *Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000; 30:1144-50.*
6. *Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity questionnaire. Allergy 1999;54:999-1003.*
7. *Brochow K, Romano A, Blanca M, Ring J, Pichler WJ, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.*
8. *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;58:854-63.*
9. *Torres MJ, Blanca M, Fernandez J, Romano A, de Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy 2003;58: 961-72.*
10. *Blanca M, Vega M, Garcia J, Carmona MJ, Terados S, Avila MJ, et al. Allergy to penicillin with good tolerance to other penicillins; study of the incidence in subjects allergic to betalactams. Clin Exp Allergy 1990; 20:475-81.*
11. *Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnostic of non-immediate reactions to beta-lactam antibiotics. Allergy 2004;59: 1153-60.*
12. *Mertes PM, Laxenaire MC, Lienhart A, SFAR, Aberer W, Ring J, Pichler WJ, Demoly P for ENDA/EAACI. Reducing the risk of anaphylaxis during anaesthesia : guidelines for clinical practice. J Invest Allergol Clin Immunol 2005;15:91-101.*
13. *Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, et al. Management of hypersensitivity reactions to iodinated contrast media. Allergy 2005;60:150-8.*
14. *Demoly P, Bousquet J. Drug allergy diagnosis work up. Allergy 2002;57:37-40.*

15. *Benahmed S, Picot MC, Dumas F, Demoly P. Clinical history is not sufficient to diagnose drug hypersensitivity reactions. Diagnostic accuracy of a pharmacovigilance algorithm. Arch Intern Med 2005;165:1500-5.*
16. *Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med 2004;141:16-22.*
17. *Stevenson DD. Challenge procedures in detection of reactions to aspirin and non-steroidal anti-inflammatory drugs. Ann Allergy 1993;71:117-8.*
18. *Dahlen B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. N Engl J Med 2000;344:142.*
19. *Torres MJ, Mayorga C, Leyva L, Guzman A, Cornejo-García JA, Juarez C, et al. Controlled administration of penicillin to patients with a positive history but negative skin and specific serum IgE tests. Clin Exp Allergy 2002;32:270-6.*
20. *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.*