

Editorial

Drug allergy and hypersensitivity: still a hot topic

**P.-J. Bousquet^{1,2}, P. Demoly^{2,3}
& A. Romano^{4,5}**

¹Département de Biostatistique, Epidémiologie Clinique, Santé Publique et Information Médicale, GHU Caremeau, Place Professeur Robert Debre, Nîmes cedex, France; ²Exploration des allergies, Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier cedex, France; ³Unité INSERM U657, Hôpital Arnaud de Villeneuve, Montpellier cedex, France; ⁴Department of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus, Rome; ⁵IRCCS Oasi Maria S.S., Troina, Italy

Philippe-Jean Bousquet
Département de Biostatistique
Epidémiologie Clinique
Santé Publique et Information Médicale
GHU Caremeau
Place Professeur Robert Debre
30 029 Nîmes cedex
France

Accepted for publication 24 November 2008

Drug allergy and hypersensitivity have been recognized for decades, but there are still large gaps in our knowledge. First, new therapeutic agents have been introduced and some, such as biological agents, are inducing adverse drug reactions (ADRs). Impurities in drugs are becoming more common, because the raw materials are not always well characterized or may be fraudulent. These impurities can also cause severe ADRs. Finally, more knowledge is needed for an improved diagnosis and treatment of drug allergy and hypersensitivity. In the present issue of this Journal, new information has been gathered on drug allergy and hypersensitivity which should be put in the context of recent publications.

Biologicals are a relatively new class of medicines that carry specific risk, in particular hypersensitivity and allergy (1). An important study attempted to determine the nature, frequency and timing of safety-related regulatory actions for biologics following approval in the United States and/or the European Union (2). A total of 174 biologics were approved and safety-related regulatory actions were decided for 41 (23.6%). The nature of safety problems identified after approval for biologics is often related to their immunomodulatory effect (infections) and

hypersensitivity reactions. Cetuximab, a chimeric mouse-human IgG₁ monoclonal antibody against the epidermal growth factor receptor, has a high prevalence of hypersensitivity reactions in some areas of the United States and has been associated with serum specific IgE for galactose- α -1,3-galactose (3). Positive skin tests to TNF- α blocking agents can be found in patients with local reactions at the injection site (4), suggesting an IgE-mediated mechanism.

In 2008, certain lots of heparin were associated with anaphylactic like reactions resulting from contamination with oversulphated chondroitin sulphate (OSCS). Low-molecular weight heparins obtained by chemical and enzymatic depolymerization of heparin are also concerned (5). Several deaths have been reported after large doses of intravenous heparin administration. The activation of the contact system has been proposed for a potential biologic link between OSCS and the observed clinical adverse events (6–8). OSCS can directly activate the kinin–kallikrein pathway in human plasma, which can lead to the generation of bradykinin, a potent vasoactive mediator. In addition, OSCS induced generation of C3a and C5a, potent anaphylatoxins derived from complement proteins.

The links between anaphylaxis and mastocytosis have been reviewed in a series of patients (9). Both adults and children with extensive skin disease with mastocytosis have an increased risk to develop severe anaphylactic reactions, including ones to drugs; thus, an emergency medicine kit with epinephrine/adrenaline is recommended for such subjects.

In 2008, hypersensitivity or allergic reactions to new drugs such as oseltamivir (10) were recognized. Because anaphylactic reactions have been observed (11), the safety of traditionally prescribed drugs is debated. Contact allergy to topical antifungal agents is not uncommon (12). On the basis of the latest literature data (13), we recommend avoiding oat-containing emollients in children with atopic dermatitis.

The diagnosis of drug allergy and hypersensitivity still needs to be improved. Patients with a history of penicillin allergy pose a treatment dilemma. Unnecessary avoidance of this relatively nontoxic class of drugs exposes the patient to often less effective and potentially more toxic drugs, increases healthcare costs, and contributes to the development of antibiotic resistance (14). Although many studies concerning the diagnosis of penicillin allergy have been carried out since the 1960s (15), such diagnosis is still a hot topic. Skin tests are recommended for the diagnosis of immediate-type reactions. In this issue of the Journal, it has been confirmed that benzylpenicillin skin testing is still useful in diagnosing immediate hypersensitivity to penicillins (16). However, anaphylactic reactions can occur after β -lactam skin test (17). Therefore, a biological diagnosis of penicillin is still needed in order to reduce the frequency of such reactions and improve the sensitivity of the allergologic work-up (18). The basophil activation test is an interesting method in β -lactam allergy diagnosis (19), but needs to be fully validated before it is proposed for routine use. Two basophil activation markers, CD63 and CD203c, can be used in the diagnosis of amoxicillin allergy (20). Administration of meropenem to penicillin-allergic patients who might benefit from this treatment is usually avoided. However, recent studies have demonstrated a very low rate of cross-reactivity between penicillins and both meropenem and imipenem in adults (21, 22). A low rate of cross-reactivity between penicillins and meropenem has also been found in children (23). Therefore, the practice of avoiding these carbapenems in subjects with IgE-mediated hypersensitivity to penicillins could be abandoned (21–23). Non-immediate reactions to β -lactams are complex, and the diagnostic value of skin testing and drug provocation tests has been compared (24). In this issue of the Journal, Blanca et al. propose a European Network for Drug Allergy (ENDA, the European Academy of Allergology and Clinical Immunology interest group on drug hypersensitivity) updates in the diagnosis of β -lactam allergy (25). CD69 upregulation on T cells is an *in vitro* marker for delayed-type drug hypersensitivity (26), but its role in daily

practice needs more studies. Radiocontrast media can induce allergic reactions, and the results of a European multicentric study on skin tests are reported in this issue (27).

The diagnosis of drug allergy and hypersensitivity needs to be standardized. The diagnosis of allergic reactions to many drugs has been standardized by the ENDA and standard operating procedures (SOPs) have been published. The ENDA was initiated as a FP3 EU project and has been self-sustainable following EU funding. It has always worked under the aegis of the European Academy of Allergology and Clinical Immunology. This network is unique in the world.

Moreover, allergic ADRs are not easily determined and need a specific diagnostic work-up, as shown by the inaccuracy of pharmacovigilance algorithms (28). There is, therefore, a need for a specific database with SOPs on drug allergy and hypersensitivity. The GALENDA project described in this issue uses a pharmacovigilance/pharmacoepidemiology database on drug allergy/hypersensitivity – established under FileMaker® Pro 9 (Drug Allergy and Hypersensitivity Database) – and is based on a sustainable FP6 Network of excellence [Global Allergy and Asthma European Network; GA²LEN (29)] in order to obtain the optimal diagnosis of the patients using ENDA SOPs. Such database is already available online in many different languages and can be accessed using a personal login. Interacting with a pharmacovigilance network, this platform appears to be of great interest for the reporting of allergy/hypersensitivity ADRs in conjunction with other pharmacovigilance instruments. Moreover, GALENDA will use GA²LEN expertise in the dissemination of results to all stakeholders, including physicians, patients (with EFA-European Federation of Allergy and Airways Diseases Patients' Associations), media and government officials to increase awareness and optimal reporting of drug allergy/hypersensitivity, which is often greatly underestimated and poorly reported.

Aspirin hypersensitivity is still an important research field. Systemic responses have been found after aspirin bronchial challenges (30). A definitive diagnosis of aspirin-exacerbated respiratory diseases requires a positive aspirin challenge, but predicting which patients will have positive challenges is often difficult. Age under 40 years, poor sense of smell, multiple prior respiratory reactions and severe prior asthmatic reactions associated with aspirin and other NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) significantly increased the chances of a positive oral aspirin challenge (31). Triflusal (an antiplatelet drug) and etoricoxib may not be safe in patients with aspirin-exacerbated respiratory diseases (32, 33). The daily dose of aspirin in desensitization in aspirin-sensitive asthmatics with nasal polyps is still a matter of debate. In one study, it was found that aspirin desensitization followed by 300-mg aspirin daily is efficacious, whereas a daily dose of 100-mg daily is not sufficient to significantly reduce nasal and bronchial symptoms (34).

The diagnosis and management of HIV drug hypersensitivity has been reviewed (35). Drug hypersensitivity reactions are an important cause of morbidity in HIV-infected patients with complex medication regimens. Correct diagnosis and management of these reactions are essential in the clinical care of HIV disease. Trimethoprim-sulfamethoxazole, abacavir, nevirapine, atazanavir and enfuvirtide can all cause hypersensitivity eruptions. In the aforesaid review (35), the authors discuss the evidence for immunological mechanisms of hypersensitivity reactions to HIV drugs, the clinical characteristics of these reactions, and the guidelines that currently exist for their identification and management.

Many anaphylactic reactions are caused by drugs (36), in particular in children (37). The treatment of anaphylaxis has been widely reviewed in recent years, and in particular in this Journal (38, 39). In this issue, Sheikh et al. (40) perform a systematic review, using the Cochrane system to assess the role of adrenalin for the treatment of anaphylaxis.

Research questions are of great importance for understanding and managing drug allergy and hypersensitivity. These questions have been addressed in this Journal recently (41–44), and may form the basis for future collaborative research.

References

1. Bousquet J, Chiron R, Humbert M. Biologics in asthma: difficulties and drawbacks. *Expert Opin Biol Ther* 2008;**8**:1921–1928.
2. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, Schellekens H, Leufkens HG, Egberts AC. Safety-related regulatory actions for biologicals approved in the United States and the European Union. *JAMA* 2008;**300**:1887–1896.
3. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M et al. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med* 2008;**358**:1109–1117.
4. Benucci M, Manfredi M, Demoly P, Campi P. Injection site reactions to TNF- α blocking agents with positive skin tests. *Allergy* 2008;**63**:138–139.
5. Zhang Z, Weiwer M, Li B, Kemp MM, Daman TH, Linhardt RJ. Oversulfated chondroitin sulfate: impact of a heparin impurity, associated with adverse clinical events, on low-molecular-weight heparin preparation. *J Med Chem* 2008;**51**:5498–5501.
6. Kishimoto TK, Viswanathan K, Ganguly T, Elankumaran S, Smith S, Pelzer K et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008;**358**:2457–2467.
7. Greinacher A, Warkentin TE. Contaminated heparin. *N Engl J Med* 2008;**359**:1291–1292; author reply 3.
8. Kakkar AK, Bonnefoi M. Contaminated heparin. *N Engl J Med* 2008;**359**:1292–1293; author reply 3.
9. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;**63**:226–232.
10. Hirschfeld G, Weber L, Renkl A, Scharffetter-Kochanek K, Weiss JM. Anaphylaxis after Oseltamivir (Tamiflu) therapy in a patient with sensitization to star anise and celery-carrot-mugwort-spice syndrome. *Allergy* 2008;**63**:243–244.
11. Hur GY, Choi GS, Park HJ, Ye YM, Park HS. Anaphylactic shock induced by *Codonopsis lanceolata*, traditional Chinese medicine in a patient with allergic rhinitis. *Allergy* 2008;**63**:1406–1407.
12. de Padua CA, Uter W, Geier J, Schnuch A, Effendy I. Contact allergy to topical antifungal agents. *Allergy* 2008;**63**:946–947.
13. Goujon-Henry C, Hennino A, Nicolas JF. Do we have to recommend not using oat-containing emollients in children with atopic dermatitis? *Allergy* 2008;**63**:781–782.
14. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 2008;**121**:572–576.
15. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. *Bull World Health Organ* 1968;**38**:159–188.
16. Romano A et al. Benzylpenicillin skin testing is still important in diagnosing immediate hypersensitivity reactions to penicillin. *Allergy* 2009;**64**:249–253.
17. Weber-Mani U, Pichler WJ. Anaphylactic shock after intradermal testing with betalactam antibiotics. *Allergy* 2008;**63**:785.
18. Kvedariene V, Demoly P. The need for a biological diagnosis of penicillin allergy. *Clin Exp Allergy* 2008;**38**:869–871.
19. de Weck AL, Sanz ML, Gamboa PM, Aberer W, Bienvenu J, Blanca M et al. Diagnostic tests based on human basophils: more potentials and perspectives than pitfalls. *Int Arch Allergy Immunol* 2008;**146**:177–189.
20. Abuaf N, Rostane H, Rajoely B, Gaouar H, Autegarden JE, Leynadier F et al. Comparison of two basophil activation markers CD63 and CD203c in the diagnosis of amoxicillin allergy. *Clin Exp Allergy* 2008;**38**:921–928.
21. Romano A, Viola M, Guéant-Rodriguez RM, Gaeta F, Valluzzi R, Guéant JL. Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med* 2007;**146**:266–269.
22. Romano A, Viola M, Guéant-Rodriguez RM, Gaeta F, Pettinato R, Guéant JL. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med* 2006;**354**:2835–2837.
23. Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy* 2008;**63**:237–240.
24. Padial A, Antunez C, Blanca-Lopez N, Fernandez TD, Cornejo-Garcia JA, Mayorga C et al. Non-immediate reactions to beta-lactams: diagnostic value of skin testing and drug provocation test. *Clin Exp Allergy* 2008;**38**:822–828.
25. Torres M et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009;**64**:183–193.
26. Beeler A, Zaccaria L, Kawabata T, Gerber BO, Pichler WJ. CD69 upregulation on T cells as an in vitro marker for delayed-type drug hypersensitivity. *Allergy* 2008;**63**:181–188.
27. Brockow K et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study. *Allergy* 2009;**64**:234–241.

28. Benahmed S, Picot MC, Dumas F, Demoly P. Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. *Arch Intern Med* 2005;**165**:1500–1505.
29. Van Cauwenberge P, Watelet JB, Van Zele T, Bousquet J, Burney P, Zuberbier T. Spreading excellence in allergy and asthma: the GA2 LEN (Global Allergy and Asthma European Network) project. *Allergy* 2005;**60**:858–864.
30. Makowska JS, Grzegorzczak J, Bienkiewicz B, Wozniak M, Kowalski ML. Systemic responses after bronchial aspirin challenge in sensitive patients with asthma. *J Allergy Clin Immunol* 2008;**121**:348–354.
31. Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD. Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008;**100**:420–425.
32. Fraj J, Valero A, Vives R, Perez I, Borja J, Izquierdo I et al. Safety of triflusal (antiplatelet drug) in patients with aspirin-exacerbated respiratory diseases. *Allergy* 2008;**63**:112–115.
33. Koschel D, Cardoso C, Leucht V, Hoffken G. Asthmatic reaction induced by Etoricoxib in a patient with aspirin-sensitive asthma. *Allergy* 2008;**63**:1093–1094.
34. Rozsasi A, Polzehl D, Deutsche T, Smith E, Wiesmiller K, Riechelmann H et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy* 2008;**63**:1228–1234.
35. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. *J Allergy Clin Immunol* 2008;**121**:826–832.e5.
36. Simon MR, Mulla ZD. A population-based epidemiologic analysis of deaths from anaphylaxis in Florida. *Allergy* 2008;**63**:1077–1083.
37. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;**63**:1071–1076.
38. Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008;**63**:1061–1070.
39. Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD et al. Practical allergy (PRACTALL) report: risk assessment in anaphylaxis. *Allergy* 2008;**63**:35–37.
40. Sheikh A et al. Adrenaline (epinephrine) for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2009;**64**:204–212.
41. Bousquet J, Bieber T, Fokkens W, Kowalski ML, Humbert M, Niggemann B et al. Important questions in allergy: novel research areas. *Allergy* 2008;**63**:143–147.
42. Demoly P, Pichler W, Pirmohamed M, Romano A. Important questions in Allergy: 1 – drug allergy/hypersensitivity. *Allergy* 2008;**63**:616–619.
43. Dibern DA Jr, Montanaro A. Allergies to sulfonamide antibiotics and sulfur-containing drugs. *Ann Allergy Asthma Immunol* 2008;**100**:91–100; quiz 3, 11.
44. Mitka M. Emergency departments see high rates of adverse events from antibiotic use. *JAMA* 2008;**300**:1505–1506.