

Position Paper

Pharmacovigilance of drug allergy and hypersensitivity using the ENDA–DAHD database and the GA²LEN platform. The Galenda project

Nonallergic hypersensitivity and allergic reactions are part of the many different types of adverse drug reactions (ADRs). Databases exist for the collection of ADRs. Spontaneous reporting makes up the core data-generating system of pharmacovigilance, but there is a large under-estimation of allergy/hypersensitivity drug reactions. A specific database is therefore required for drug allergy and hypersensitivity using standard operating procedures (SOPs), as the diagnosis of drug allergy/hypersensitivity is difficult and current pharmacovigilance algorithms are insufficient. Although difficult, the diagnosis of drug allergy/hypersensitivity has been standardized by the European Network for Drug Allergy (ENDA) under the aegis of the European Academy of Allergology and Clinical Immunology and SOPs have been published. Based on ENDA and Global Allergy and Asthma European Network (GA²LEN, EU Framework Programme 6) SOPs, a Drug Allergy and Hypersensitivity Database (DAHD[®]) has been established under FileMaker[®] Pro 9. It is already available online in many different languages and can be accessed using a personal login. GA²LEN is a European network of 27 partners (16 countries) and 59 collaborating centres (26 countries), which can coordinate and implement the DAHD across Europe. The GA²LEN–ENDA–DAHD platform interacting with a pharmacovigilance network appears to be of great interest for the reporting of allergy/hypersensitivity ADRs in conjunction with other pharmacovigilance instruments.

P.-J. Bousquet^{1,2*,†}, P. Demoly^{1*,†}, A. Romano^{3,4*,†}, W. Aberer⁵, A. Bircher⁶, M. Blanca⁷, K. Brockow⁸, W. Pichler⁹, M. J. Torres⁷, I. Terreehorst¹⁰, B. Arnoux², M. Atanaskovic-Markovic¹¹, A. Barbaud¹², A. Bijl¹³, P. Bonadonna¹⁴, P. G. Burney¹⁵, S. Caimmi^{2*}, G. W. Canonica¹⁶, J. Cernadas¹⁷, B. Dahlen^{18*}, J.-P. Daures¹, J. Fernandez¹⁹, E. Gomes²⁰, J.-L. Gueant²¹, M. L. Kowalski²², V. Kvedariene²³, P.-M. Mertes²⁴, P. Martins²⁵, E. Nizankowska-Mogilnicka²⁶, N. Papadopoulos²⁷, C. Ponvert²⁸, M. Pirmohamed²⁹, J. Ring⁸, M. Salapatas^{30*}, M. L. Sanz³¹, A. Szczeklik²⁶, E. Van Ganse³², A. L. De Weck³¹, T. Zuberbier³³, H. F. Merk³⁴, B. Sachs³⁴, A. Sidoroff³⁵, Global Allergy, Asthma European Network (GA²LEN) and Drug Allergy and Hypersensitivity Database (DAHD) and the European Network for Drug Allergy (ENDA)

¹Département de Biostatistique Epidémiologie Clinique, Santé Publique et Information Médicale, GHU Carémeau, CHU Nîmes, Nîmes cedex 9, France;

²Exploration des Allergies, Hôpital Arnaud de Villeneuve, CHU Montpellier, Montpellier cedex 5, France;

³Department of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus, Rome, Italy; ⁴IRCCS Oasi Maria S.S., Troina, Italy; ⁵Medizinische Universität Graz, Graz, Austria;

⁶Allergy Unit, University Hospital Basel, Basel, Switzerland; ⁷Research Unit for Allergic Diseases, Allergy Service, Carlos Haya Hospital, Malaga, Spain;

⁸Department of Dermatology and Allergy Biederstein, Helmholtz Zentrum/TUM Technische Universität München, Munich, Germany; ⁹Division of Allergology, Clinic for Rheumatology and Clinical Immunology/Allergology, Inselspital, Berne, Switzerland;

¹⁰Amsterdam University, the Netherlands; ¹¹University Children's Hospital, Belgrade, Serbia; ¹²Dermatology

Department, Fournier Hospital, Nancy, France;

¹³Nederlands Bijwerken Centrum Lareb, MH

¹⁴s-Hertogenbosch, the Netherlands; ¹⁵Allergy Service,

Verona General Hospital, Verona, Italy; ¹⁵Respiratory Epidemiology & Public Health, Imperial College, London, UK; ¹⁶Allergy & Respiratory Diseases Clinic, University of Genova, Genova, Italy; ¹⁷Allergy and Clinical Immunology Division, Hospital São João EPE, Porto, Portugal; ¹⁸Karolinska Institute, Stockholm, Sweden; ¹⁹Allergy Section, Department of Medicine, Elche Hospital, Elche, Spain; ²⁰Department of Allergy and Clinical Immunology, Centro Hospitalar do Porto – Maria Pia Unit, Porto, Portugal; ²¹Inserm U-724, Laboratoire de Pathologie Cellulaire et Moléculaire en Nutrition and Department of Clinical Biochemistry, University Hospital Centre, Nancy, France; ²²Medical University of Lodz, Lodz, Poland; ²³Vilnius University, Medical Faculty and Center of Pulmonology and Allergology, Vilnius University Hospital Santariskiu klinikos, Vilnius, Lithuania; ²⁴Service d'Anesthésie-Réanimation, Hôpital Central, Centre Hospitalier Universitaire, Nancy, France; ²⁵University of Lisbon, Portugal; ²⁶Jagiellonian University School of Medicine, Krakow, Poland; ²⁷Allergy Research Center, University of Athens, Athens, Greece; ²⁸Hôpital Necker, Paris, France; ²⁹Department of Pharmacology, University of Liverpool, Liverpool, UK; ³⁰EFA, European Federation of Allergy and Airway Diseases Patients Association; ³¹Department of Allergology and Clinical Immunology, University Clinic, University of Navarra, Pamplona, Spain; ³²Pharmacoepidemiology Unit, Centre Hospitalier Universitaire, Lyon, France; ³³Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité, Berlin, Germany; ³⁴Department of Dermatology & Allergology, University Hospital of RWTH-Aachen, Germany; ³⁵Department of Dermatology and Venereology, Medical University of Innsbruck, Innsbruck, Austria

Key words: drug allergy; database; DAHD; GA²LEN; ENDA.

Philippe-Jean Bousquet
Département de Biostatistique Epidémiologie
Clinique
Santé Publique et Information Médicale
GHU Carémeau
CHU Nîmes
30 029 Nîmes cedex 9
France

*Member of GA²LEN (Global Allergy and Asthma European Network), supported by the Sixth EU Framework programme for research, contract no. FOOD-CT-2004-506378.

†The first three authors have participated equally to the paper.

Accepted for publication 30 September 2008

Abbreviations: ADR, adverse drug reaction; CDISC, Clinical Data Interchange Standards Consortium; CM, contrast media; DAHD, Drug Allergy and Hypersensitivity Database; DIHS, drug-induced hypersensitivity syndrome; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; EAACI, European Academy of Allergology and Clinical Immunology; EFA, European Federation of Allergy and Airways Disease Patients; EMEA, European Medicines Agency; ENDA, European Network for Drug Allergy; FP, EU Framework Programme; GA²LEN, Global Allergy and Asthma European Network; ICD, International Classification of Diseases; INN, International Nonproprietary Names; MedDRA, Medical Dictionary for Regulatory Activities; NCA, national competent medicines authorities; SCAR, severe cutaneous adverse reaction; SOP, standard operating procedure.

Adverse drug reactions (ADRs) encompass all adverse events related to drug administration, regardless of aetiology and pathogenic mechanism. An ADR is defined by the World Health Organization as a noxious and unintended response to a drug occurring at a dose normally used in man (1). The traditional pharmacological classification of ADRs separates them into two major subtypes: type A reactions, which are dose-dependent and predictable and type B reactions, which are not dose-dependent and which are unpredictable. A majority of ADRs are of type A (2). Type B reactions comprise approximately 10–15% of all ADRs and include hypersensitivity drug reactions. According to the Nomenclature Review Committee of the World Allergy Organization, the term 'hypersensitivity' should be used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. This Committee also distinguishes allergic hypersensitivity reactions from nonallergic ones. Drug allergy refers to a hypersensitivity reaction where a definite immunological mechanism, either IgE or T-cell mediated, is demonstrated, while nonallergic hypersensitivity refers to reactions, such as those to acetylsalicylic acid, in which other pathogenic mechanisms play a role (3). Therefore, the terms 'drug allergy' and 'drug hypersensitivity' should not be used interchangeably. 'Drug allergy' should be used only for an ADR in which an immunological mechanism has been demonstrated (4). In contrast, drug hypersensitivity is a much broader term with extremely diverse presentation, including IgE-mediated allergic reactions in the form of immediate anaphylactic shock or generalized urticaria and/or angioedema and/or bronchospasm (4) as well as nonimmunological reactions and nonimmediate reactions, which typically occur several days after the eliciting drug administration (5–7). These late reactions are extremely polymorphic and occur in the form of urticaria, maculopapular eruptions, fixed drug eruptions, acute generalized exanthematic pustulosis, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). A classification has been recently proposed for biological agents (8).

Adverse drug reactions affect 10–20% of hospitalized patients and more than 7% of the general population. They represent more than 15% of all ADRs (9). They may be potentially life-threatening, prolong hospitalization, affect the drug prescribing patterns of physicians and result in socioeconomic costs. Moreover, they are one of the main causes for drug withdrawal from the market and thus of great financial importance for the pharmaceutical industry. Apart from the ongoing Regiscar project, which focuses on severe cutaneous reactions (10–12) only, as well as a few national continuous surveys such as the French Groupe d'étude des réactions anaphylactoides peranesthésiques survey

on anaphylaxis during general anaesthesia (13), well-designed epidemiological studies on drug hypersensitivity reactions are lacking as most studies have focused on ADRs in general. A connection between clinical manifestations and drug intake is rarely proven and both under-diagnosis and over-diagnosis must be taken into account. Severe reactions including anaphylaxis, drug hypersensitivity syndromes, DRESS/DIHS, Stevens-Johnson syndrome/toxic epidermal necrolysis, vasculitis and hepatitis are also associated with significant morbidity and mortality.

Databases exist for the collection of ADRs. Spontaneous reporting forms the core data-generating system of pharmacovigilance, relying on healthcare professionals (and in some places consumers) to identify and report any suspected ADR (14). One of this system's major weaknesses is under-reporting (15), though the figures vary greatly between countries and in relation to minor and serious ADRs. Another problem is that medical personnel do not always consider reporting as a priority if the symptoms are not serious and ADRs may not be recognized as the effect of a particular drug (16). Moreover, allergic ADRs are not easily determined and need a specific diagnosis work-up as shown by the inaccuracy of pharmacovigilance algorithms (17).

There is therefore a need for a specific database on drug allergy and hypersensitivity using standard operating procedures (SOPs), as the diagnosis of drug allergy/hypersensitivity is difficult (18) and current pharmacovigilance algorithms are insufficient (17).

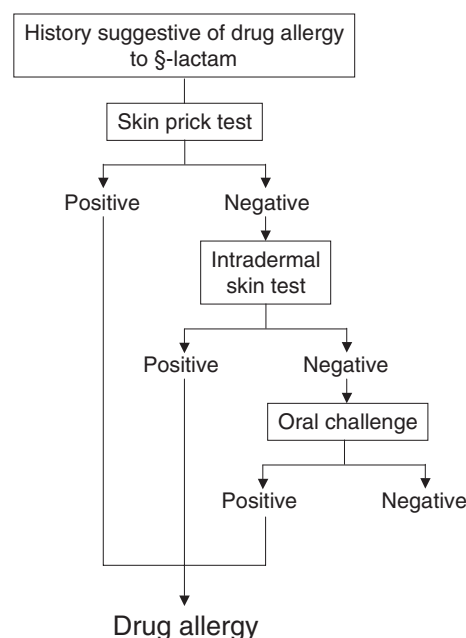


Figure 1. Diagnostic work up of immediate drug allergy to β-lactams.

ENDA and GA²LEN SOPs for the diagnosis of drug allergy and hypersensitivity

The patient's history is fundamental in the diagnosis of drug allergy/hypersensitivity and the allergological examination includes *in vivo* and *in vitro* tests selected on the basis of clinical features (18). Prick, intradermal and patch tests are the most readily available forms of allergy testing but, for many drugs, have not been standardized. The determination of specific IgE levels is still the most widely accessible *in vitro* method for diagnosing immediate reactions. However, as most drugs cannot be tested, this method is available only for a few drugs and its sensitivity is

often insufficient. The basophil activation test and the lymphocyte proliferation assays test may increase the sensitivity of diagnostic work-ups, but more data are required to allow their use in routine. There is an urgent need to obtain appropriate reagents for the diagnosis of drug allergy/hypersensitivity (19). In many patients, provocation tests are needed to confirm the diagnosis.

Although difficult, the allergy diagnosis of reactions to many drugs has been standardized by the European Network for Drug Allergy (ENDA) of the European Academy of Allergy and Clinical Immunology (EAACI, <http://www.eaaci.net>) and SOPs have been published (Fig. 1). ENDA was initiated as a EU Framework

DRUG HYPERSENSITIVITY

INVESTIGATOR:
 Name: Center:
 Address: Tel/Fax/E-mail:
 Protocol No:
 Date of protocol:

PATIENT:
 Name: Date of birth: Age: years
 Weight: kg Height: cm
 Profession: Origin: Sex: ☐ M ☐ F
 Risk groups: ☐ Medical staff ☐ Pharmaceutical Industries ☐ Farmers ☐ others/specify:

CURRENT COMPLAINTS:

DRUG REACTION:
 (Multiple boxes can be ticked; underline the choice if necessary; chronology can be characterized with numbers)
☐ **CUTANEOUS SYMPTOMS:**
☐ Maculopapular exanthema
☐ Macular exanthema
☐ Urticarious exanthema
☐ AGEP (Acute generalized exanthematous pustulosis)
☐ Eczematoid exanthema
☐ Erythema exudativum multiforme
☐ Bullous exanthema
☐ Stevens Johnson Syndrome / TEN (M. Lyell)
☐ Fixed drug exanthema
☐ Purpura -> Thrombocyte count
 ☐ palpable ☐ haemorrhagic-necrotizing
 ☐ Visceral organ involvement:
☐ Contact dermatitis ☐ Topic cause ☐ Haematogenous cause ☐
☐ Urticaria vasculitis
☐ ONLY Pruritus
☐ Urticaria
☐ Angioedema/Location/s:
☐ Conjunctivitis
☐ Other/Specification:
☐ Morphology/Location/s:
☐ EFFLORESCENCES: Distribution / Dynamics (↑ ↓)

DATE OF REACTION:
☐ **DIFFERENTIAL DIAGNOSIS:**
☐
☐
☐
☐ **CONTRIBUTING FACTORS:**
☐ Viral infections: ☐ Flu like infection ☐ Other:
☐ Fever
☐ Suspicion of photosensitivity ? ☐ No ☐ Yes ☐ Unknown
☐ Stress
☐ Exercise
☐ Other/Specification:
☐ **EVOLUTION:**
Intensity

 h / days

☐ **generalized**

GASTROINTESTINAL AND RESPIRATORY SYMPTOMS:
☐ Nausea/Emesis
☐ Diarrhea
☐ Gastro intestinal cramps
☐ Cough
☐ Dysphonia
☐ Dyspnea PEFr or FEV1:
☐ Wheezing/Bronchospasm
☐ Rhinitis
☐ Rhinorrhea
☐ Sneezing
☐ Nasal obstruction
☐ Other/Specification:
☐ **PSYCHIC SYMPTOMS:**
☐ Fear/Panic reaction ☐ Vertigo

ASSOCIATED SYMPTOMS:
☐ Involvement of: ☐ Liver ☐ Kidney ☐ Other/Specification:
☐ Fever °C
☐ Malaise
☐ Pain/Burning ☐ Location/s:
☐ Edema ☐ Location/s:
☐ Arthralgia/Myalgia ☐ Location/s:
☐ Lymphadenopathy
☐ Other/Specification:
☐ **CARDIOVASCULAR SYMPTOMS:**
☐ Tachykardia Pulse rate:/min
☐ Hypotension Blood pressure: mmHg
☐ Collapse
☐ Arrhythmia
☐ Other/Specification:
☐ **INVOLVEMENT OF OTHER ORGANS:**

Figure 2. ENDA questionnaire.

Programme 3 (FP3 EU) project and has been self-sustainable following EU funding. This network is unique in the world and is linked with the EAACI Drug Allergy Interest Group focusing on improvement in diagnosing patients with drug allergy/hypersensitivity. Moreover, it helps in the organization of drug allergy teaching within EAACI and undertakes collaborative research. It involves several groups from all over Europe.

For an accurate diagnosis, the method shown in Fig. 1 was proposed. A detailed history is of paramount importance as to whether a certain disease reflects drug hypersensitivity and regarding the question of which drug is causing the reaction. To facilitate the recording of an appropriate history and to harmonize this procedure in Europe, the members of ENDA have developed a questionnaire, which provides a standardized guide in this difficult area of clinical medicine (20). It takes only about 5–6 min to complete this standardized protocol which has been translated into many languages (Fig. 2) and which is available online (<http://www.eaaci.net>). The questionnaire is a practical compromise, as it combines questions and investigations which are important for the acute as well as remission stages. It emphasizes the clinical status (skin and internal involvement) and includes some laboratory markers available in all clinical laboratories that are of potential interest in drug hypersensitivity reactions (blood differential, liver and kidney parameters). These aspects of the history and the examinations represent a common denominator within the different European centres using this protocol.

Skin tests represent an essential tool for the diagnosis of drug allergy, although many drugs cannot be tested (21–23). The standardized procedure for immediate skin tests to β -lactams, the most common class of drug-induced allergic reactions, has been published by ENDA (22, 24, 36). Particular caution should be taken during testing, starting with the appropriate dilutions of the stock reagents, as some systemic reactions have been observed during skin tests (25).

In vitro tests can be used in drug allergy/hypersensitivity, but they are usually less sensitive and/or specific than those used for inhalant allergy (26). There has been some progress for detecting specific IgE to chlorhexidine or rocuronium, but these commercially-available methods for IgE detection are still quite limited and their relevance is unclear (27). Although promising, some cellular tests, such as histamine release, basophil activation (28, 29), cysteinyl-leukotriene release or T-cell based assays (proliferation, activation) (30, 31), are interesting research tools. Their sensitivity and specificity vary across centres and still require further validation.

The standardized methodology for drug provocation tests (DPTs), the controlled administration of a drug to diagnose drug allergy/hypersensitivity reactions, has been published by ENDA (32). An accurate identification of the agent inducing a patient's hypersensitivity reaction is important, as the consequences of the diagnosis can be

severe. Confirmation of a presumptive diagnosis by a DPT is often the only reliable way to establish a diagnosis. This procedure should only be undertaken with great caution and a compelling need, as DPTs can also cause life-threatening reactions. As a consequence, they are not suitable for many situations. The test performance should follow established criteria and respect the many limitations, potentially leading to false-positive or false-negative test results. Finally, for delayed reactions, protocols are still not standardized.

Causality and imputation must follow defined rules. The 'WHO Drug Monitoring Program' suggests the following terms: certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable (33). However, even a negative DPT is not an absolute guarantee for tolerance. Altogether, drug allergy diagnosis does not have a 100% predictive value and must be relied on combination of history, *in vivo* and *in vitro* tests. Moreover, they may not necessarily predict absolute life-long tolerance upon future exposure (as proven in food allergy testing).

The methodology for provocation tests with aspirin and nonsteroidal anti-inflammatory agents follows the GA²LEN-EAACI guidelines (34).

Nonimmediate manifestations (i.e. occurring more than 1 h after drug administration), particularly maculopapular and urticarial eruptions, are common, especially during β -lactam treatment (35). The mechanisms involved in most nonimmediate reactions seem to be heterogeneous and are not yet all completely understood (36). However, clinical and immunohistological studies, as well as the analysis of drug-specific T-cell clones obtained from the circulating blood and the skin, suggest that a type-IV (cell-mediated) pathogenic mechanism may be involved in many nonimmediate reactions such as maculopapular or bullous eruptions and acute generalized exanthematous pustulosis (5, 6). In the ENDA diagnostic algorithm for evaluating nonimmediate reactions to β -lactams (36), both patch tests and delayed-reading intradermal tests are proposed. In the case of negative results in such tests, consideration should be given to provocation tests and to the careful administration of the suspect agents. With regard to *in vitro* tests, the lymphocyte transformation test may contribute to the identification of the responsible drug, but is not widely available.

All iodinated contrast media (CM) are known to cause both immediate (≤ 1 h) and nonimmediate (> 1 h) hypersensitivity reactions (37). Although allergic hypersensitivity cannot be demonstrated for most immediate reactions, recent studies indicate that the severe immediate reactions may be IgE-mediated, while most of the nonimmediate exanthematous skin reactions appear to be T-cell mediated. Patients who experience such hypersensitivity reactions are therefore advised to undergo allergological evaluation. Several investigators have found skin testing to be useful in confirming a CM allergy, especially in patients with nonimmediate skin eruptions (38). ENDA has also

provided information on the diagnosis and prevention of hypersensitivity reactions to iodinated CM (37).

Severe and sometimes fatal reactions to general anaesthetics may occur. The diagnosis of these reactions follows the guidelines of the Société Française d'Anesthésiologie et de Réanimation published in collaboration with ENDA (39).

The DAHD[®] based on ENDA

The Drug Allergy and Hypersensitivity Database (DAHD[®]) is a historical prospective, mixed cohort, which was developed in the Allergy Department of the Montpellier University Hospital in collaboration with INSERM. As an epidemiological and pharmacovigilance tool, DAHD was designed to store information on patients having undergone a standardized procedure of drug allergy/hypersensitivity diagnosis following the ENDA recommendations (20, 22, 32, 36, 37). After a detailed clinical history, patients with a compatible history of drug allergy/hypersensitivity are tested in the absence of any contraindication. Depending on the drugs, patients undergo skin tests (prick tests, intradermal tests), *in vitro* tests and then allergen challenges. For cutaneous drugs, patch tests are also performed. Those with a severe cutaneous reaction (toxic epidermal necrolysis or Stevens-Johnson syndromes), vasculitis, multi-organs failure including DRESS are not challenged because of possible serious, systemic and uncontrollable events (40–42). The work up in these reactions should be standardized, starting with *in vitro* tests and limited to patch tests at the lowest reagent concentrations (only when an alternative is not available). At the end of the procedure, patients are identified as 'sensitive' or 'not sensitive' to the tested drugs (suspected and alternative ones). There is also the Project on Severe Cutaneous Adverse Drug Reactions (RegisCAR) (<http://regiscar.uni-freiburg.de>). This is a European Registry of severe cutaneous adverse reaction (SCAR) for the continuous surveillance of new drugs with adequate pharmacoepidemiological methods, which collects samples to study the phenotype of patients (43).

DAHD

The database was developed under FileMaker[®] Pro 9 (<http://www.filemaker.com>), allowing an easy online access (using the Internet network). The database has been translated into several languages including Dutch, French, English and Portuguese and can be translated into any other language as required. The choice of the platform was made to comply with the most recent standardized procedures: the Clinical Data Interchange Standards Consortium (CDISC, <http://www.cdisc.org>) standard, even if DAHD is not a clinical trial database. The CDISC has been developed to support global, platform-independent data standards that enable information system interoperability

to improve medical research and related areas of health care. It integrates Food and Drug Administration and European Medicines Agency (EMA) recommendations on databases. As with all databases, it promotes consistent data entry and retrieval, and reduces the existence of duplicate data among the database tables.

Security and privacy of the patient

Drug Allergy and Hypersensitivity Database is available online using a personal login and a centre affiliation. This access can be restricted to a read-only. To ensure confidentiality of the information and a higher security level, only the DAHD administrator can access the entire database. However, a country coordinator can access data from a single country after acceptance from the other country centres. Additionally, it is not possible to export data (i.e. in a comma separated value or text file) using an on-line access. This function is restricted to the DAHD administrator, guarantying an optimal level of security. DAHD is an anonymous database registered by the *Comité National Informatique et Liberté* (<http://www.cnil.fr>), the French regulatory institution for databases and electronic files. It is therefore impossible to access information using a name, address, patient hospital electronic folder number or national insurance number. To allow an inter-operability with the pharmacovigilance systems, each medical centre using DAHD keeps a local file linking the anonymity number to the patient's identity.

Information

This multi-table database registers demographic characteristics, atopy or asthma as well as medical histories involving a suspicion of drug allergy/hypersensitivity and all the tests performed. For each medical suspicion, the following data are collected: date, symptoms, delay between drug intake and clinical symptoms, drug names. A specific algorithm allows an automatic conversion from clinical symptoms to a symptom group such as anaphylaxis or anaphylactic shock. Finally, the date of testing, the molecule and the reactions are collected for each test. This database structure allows specific research on symptoms, symptom classes or positive tests.

Symptom terms

Drug Allergy and Hypersensitivity Database codes the ENDA questionnaire in medical terms. However, it is currently being checked as to whether these terms can be coded according to Medical Dictionary for Regulatory Activities (MedDRA) (44, 45), a clinically validated international medical terminology used by regulatory authorities in many countries. In addition, MedDRA is the adverse event classification dictionary endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for

Human Use (45). It incorporates the most important terminology dictionary, which includes the World Health Organization Adverse Reaction Terminology, regulatory-related terminology from the International Classification of Diseases (ICD), regulatory-related terminology from the ICD with clinical modification and the coding symbols for a thesaurus of adverse reaction terms. EudraVigilance®, the European Union pharmacovigilance system, uses the MedDRA terms.

Drug code

Drugs included in the database are coded using either their commercial name or their International Nonproprietary Name (INN), i.e. the scientific (active molecule) name. Additionally, each commercial name is linked to its respective INN (one or more, depending on the number of active molecules included in the drug). Finally, an internal link enables a grouping according to the drug class, for instance, nonsteroidal anti-inflammatory drug, β -lactam or penicillin/cephalosporin. Using these different links, it is possible to perform specific searches on the commercial name or on the INN drug class (Fig. 3). A search involving several countries can also be performed even if the commercial names are different between countries.

Current use

Drug Allergy and Hypersensitivity Database is used prospectively in Montpellier and involves over 3500 patients, including around 800 with positive skin tests or challenges. It has also started in Rome, Malaga and Leiden. Using these data, several studies have been published from the Montpellier data (mainly on beta-lactam allergy) (25, 27, 35, 38, 46) or as a part of a multi-centre analysis (radio-CM European survey).

Through this network, standardized questionnaires and methods will be distributed throughout Europe, optimizing diagnosis and pharmacovigilance tools. These tools will not be based on suspicion only, but also on confirmed diagnosis. At large, pharmacovigilance can be increased, reporting all cases of proven drug allergy/hypersensitivity. In accordance with European authorities, a sanitary survey can be established for newly developed drugs as well as for the older ones.

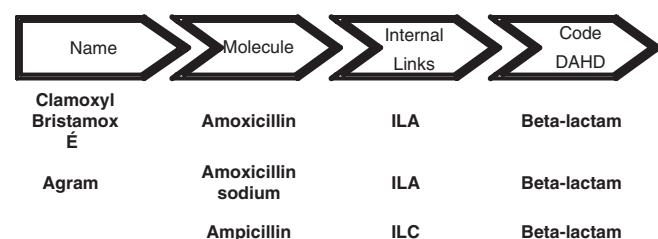


Figure 3. Drug coding.

Interactions between ENDA-DAHD and GA²LEN

Global Allergy and Asthma European Network (GA²LEN, FP6) is a European network of 27 partners (16 countries) and 59 collaborating centres (26 countries) (47). Interaction is optimal between allergists, respiratory physicians, paediatricians, ENT physicians, dermatologists, General Practitioners, epidemiologists, methodologists, basic scientists and patients. All methods needed for a project on allergy as well as asthma and related diseases are regularly used in the ongoing network and the harmonization of methods within centres has been established (2004–2009). GA²LEN uses SOPs for diagnosis, sampling procedures and exchange of samples (48, 49). A particular effort has been made to standardize methods within and between centres (49). Several networks have been established in GA²LEN. ENDA is a GA²LEN collaborating centre.

One challenge for asthma and allergy is to match the complexity of the diseases which are dependent on many factors including gene, environment and age. It is therefore necessary to have a generic platform with a network embedding all areas of Europe and all age groups. GA²LEN is presently designing a generic platform for allergy and asthma derived from the current FP6 network of excellence with key characteristics (efficiency, modularity, flexibility, expansibility, scalability and cost-effectiveness). Using modularity and flexibility, this generic platform may be used for different purposes including a network of DAHD® (Fig. 4). Flexibility will be met by a federated, multilayer architecture in which independent components, data sources, scientific services and links can be configured dynamically and articulated by rules and ethic. The GA²LEN platform allows this modularity and flexibility as it uses the same interface between modules and the same organization. Moreover, the data management to be developed will provide the system with feedback channels from the different modules with closed-loop configurations.

In each country, a GA²LEN centre will be the single DAHD® centre or coordinator of DAHD® centres. Many of these are already GA²LEN partners or collaborating centres, and any one may become a new collaborating centre. The same methodology will be used throughout Europe to diagnose and report drug allergy/hypersensitivity using the best available methods. Knowledge transfer will be needed for some centres and GA²LEN will help in the training of investigators and in the accreditation of centres using the usual procedures developed and implemented by GA²LEN. This will considerably increase the education of the personnel within all centres across Europe concerning drug allergy/hypersensitivity and adequate ADR reporting.

European Federation of Allergy and Airways Disease Patients (EFA) is a GA²LEN partner and will be actively associated with the GA²LEN-ENDA-DAHD platform.

This platform will use GA²LEN expertise in the dissemination of results to all stakeholders including

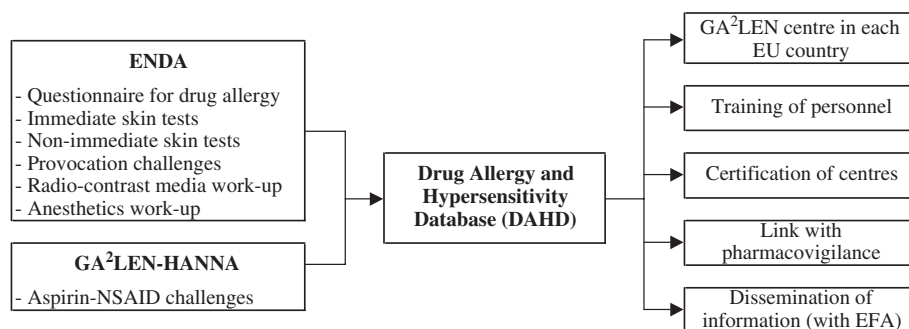


Figure 4. Interactions between ENDA–DAHD and GA²LEN correct ‘centre’ and ‘personnel’.

physicians, patients (EFA), media and politicians to increase awareness and reporting on drug allergy/hypersensitivity, which is often largely underestimated.

Interactions of the GA²LEN–ENDA–DHAD platform with pharmacovigilance networks

Pharmacovigilance is the continual monitoring of adverse effects and other safety-related aspects of marketed medications, biological products, herbal drug and traditional medicines with a view to identifying new information regarding hazards associated with medicines and preventing harm to patients. It is essential to have a thorough postmarketing surveillance system of marketed products to ensure a positive benefit: risk balance of medicines. In the past, pharmacovigilance tended to be a process focusing on spontaneous reporting, which was often insufficient to allow meaningful assessment because of under reporting and poor data quality (50).

Pharmacovigilance in Europe is coordinated by the EMEA and conducted by the national competent medicines authorities (NCA). One of the responsibilities of the EMEA is to maintain and develop the pharmacovigilance database consisting of all suspected serious adverse reactions to medicines observed in the European Union. The system, called EudraVigilance®, is a data-processing network and management system for reporting and evaluating suspected ADR during the development and following the marketing authorization of medicinal products (<http://eudravigilance.emea.europa.eu>). The EudraVigilance Post-Authorisation Module is designed for postauthorization ICSRs, Regulation (EC) No 726/2004, Directive 2001/83/EC.

Reporting is one of the limitations of pharmacovigilance, and this is particularly true for drug allergy and hypersensitivity reactions (51–57). Moreover, for drug allergy, reports are often limited to severe reactions such as anaphylaxis and anaphylactic shock or SCAR. Other reactions, like urticaria or maculopapular exanthema, which are the most common, are barely reported in pharmacovigilance databases.

Another limitation, more specific to drug allergy, is the inadequacy of pharmacovigilance algorithms (17). This

limitation is linked to several problems. First of all, clinical data can be insufficient, making the use of the algorithms impossible (lack of criteria). Additionally, it is sometimes difficult to define the culprit drug when more than one drug was taken at the time of the reaction. Moreover, drug allergy/hypersensitivity reactions can occur at any time from the onset of the treatment, even after years of use. Finally, in many cases, the clinical reaction can be either the consequence of the disease or of the drug (e.g. a maculopapular reaction during a viral infection and a concomitant use of analgesic drugs or antibiotics).

Therefore, there is a need for a complementary system to collect accurately diagnosed drug allergy/hypersensitivity reactions. This will be an important shift to a more proactive approach, requiring a broadening evidence base and a widening of expertise, resources and methodologies.

The GA²LEN–ENDA–DAHD platform interacting with a pharmacovigilance network appears to be of great interest for the reporting of drug allergy/hypersensitivity ADRs in conjunction with other pharmacovigilance instruments. The aim is to expedite the generation of more and more reliable pharmacoepidemiological data for proactive pharmacovigilance and risk management of medicines throughout their life-cycle.

European Medicines Agency is developing the European Network for Centers for Pharmacoepidemiology and Pharmacovigilance (<http://www.emea.europa.eu>) and the GA²LEN–ENDA–DHAD platform may be of interest within this network.

A change of focus is expected in pharmacovigilance, which will require the inclusion of disciplines such as advanced epidemiology, biostatistics, drug utilization, pharmacoepidemiology and the use of large automated population-based exposure-outcome databases. There is thus a pressing need to expand the knowledge of pharmacovigilance professionals to support proactive pharmacovigilance and risk management of medicines throughout their life-cycle. An understanding of pharmacovigilance is also needed for journalists and patient organizations to improve their communication of hazards associated with medicines. All these needs are already used by GA²LEN through its dissemination programmes.

Need for a network using a common database

- Although ENDA protocols are used by most major groups in Europe for the diagnosis of drug allergy/hypersensitivity reactions, a network will increase the standardization of the procedure and will also increase the number of centres using ENDA diagnosis protocols.
- There are regional/national differences regarding drug prescription.
- All drugs may induce hypersensitivity reactions, but there is a need for a network to increase the number of cases tested identically.

- A network will rapidly detect new reaction patterns (e.g. signal identification/detection).
- An exhaustive database will reinforce the epidemiological findings and risk factors.

Acknowledgments

The authors would like to thank Ms Anna Bedbrook for the revision of the paper.

References

1. WHO. International drug monitoring: the role of national centres. *Tech Rep Ser* 1972;**498**:1–25.
2. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. *Textbook of adverse drug reactions*. Oxford: Oxford University Press, 1977:10–45.
3. Johansson SG, 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**: 832–836.
4. Sanchez E, Torres MJ, Mayorga C, Reche M, Padial A, Romano A et al. Adverse drug reactions with an immunological basis: from clinical practice to basic research. *Allergy* 2002;**57**(Suppl. 72):41–44.
5. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; **139**:683–693.
6. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions – new concepts. *Clin Exp Allergy* 2007;**37**: 989–999.
7. Roujeau JC. Immune mechanisms in drug allergy. *Allergol Int* 2006;**55**:27–33.
8. Pichler WJ. Adverse side-effects to biological agents. *Allergy* 2006;**61**: 912–920.
9. Guglielmi L, Guglielmi P, Demoly P. Drug hypersensitivity: epidemiology and risk factors. *Curr Pharm Des* 2006;**12**:3309–3312.
10. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, Naldi L, Viboud C, Roujeau JC. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001;**15**:1843–1848.
11. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR study. *J Invest Dermatol* 2008; **128**:35–44.
12. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008;**58**:33–40.
13. Laxenaire MC, Mertes PM. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001;**87**:549–558.
14. Lindquist M. The need for definitions in pharmacovigilance. *Drug Saf* 2007;**30**: 825–830.
15. Edwards IR. The management of adverse drug reactions: from diagnosis to signal. *Therapie* 2001;**56**:727–733.
16. Lindquist M. Data quality management in pharmacovigilance. *Drug Saf* 2004;**27**:857–870.
17. 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.
18. Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. *Curr Opin Allergy Clin Immunol* 2007;**7**: 299–303.
19. Blanca M, Romano A, Torres MJ, Demoly P, DeWeck A. Continued need of appropriate betalactam-derived skin test reagents for the management of allergy to betalactams. *Clin Exp Allergy* 2007;**37**:166–173.
20. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy* 1999;**54**:999–1003.
21. 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.
22. 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.
23. Torres MJ, Romano A, Mayorga C, Moya MC, Guzman AE, Reche M et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy* 2001;**56**:850–856.
24. Torres MJ, Blanca M. Importance of skin testing with major and minor determinants of benzylpenicillin in the diagnosis of allergy to betalactams. Statement from the European Network for Drug Allergy concerning AllergoPen withdrawal. *Allergy* 2006;**61**:910–911.
25. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with betalactams: a risk factor analysis. *J Allergy Clin Immunol* 2006;**117**:466–468.
26. Blanca M, Mayorga C, Torres MJ, Reche M, Moya MC, Rodriguez JL et al. Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy* 2001;**56**:862–870.
27. Fontaine C, Mayorga C, Bousquet PJ, Arnoux B, Torres MJ, Blanca M et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy* 2007;**62**:47–52.

28. Kvedariene V, Kamey S, Ryckwaert Y, Rongier M, Bousquet J, Demoly P et al. Diagnosis of neuromuscular blocking agent hypersensitivity reactions using cytofluorimetric analysis of basophils. *Allergy* 2006;**61**: 311–315.
29. 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.
30. 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.
31. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy* 2004;**59**:809–820.
32. 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.
33. Venulet J, Ciucci AG, Berneker GC. Updating of a method for causality assessment of adverse drug reactions. *Int J Clin Pharmacol Ther Toxicol* 1986;**24**:559–568.
34. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczynska M, Dahlen B, Dahlen S et al. Aspirin provocation tests for diagnosis of aspirin sensitivity. *EAACI/GA²LEN guideline*. *Allergy* 2007;**62**:1111–1118.
35. Bousquet PJ, Kvedariene V, Co-Minh HB, Martins P, Rongier M, Arnoux B et al. Clinical presentation and time course in hypersensitivity reactions to beta-lactams. *Allergy* 2007;**62**: 872–876.
36. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K et al. Diagnosis of non-immediate reactions to beta-lactam antibiotics. *Allergy* 2004;**59**:1153–1160.
37. 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**:150–158.
38. Kvedariene V, Martins P, Rouanet L, Demoly P. Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period. *Clin Exp Allergy* 2006;**36**:1072–1077.
39. Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol* 2005;**15**:91–101.
40. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* 2003;**4**:561–572.
41. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996;**15**:250–257.
42. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005;**209**:123–129.
43. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;**18**:99–107.
44. Brown EG. Using MedDRA: implications for risk management. *Drug Saf* 2004;**27**:591–602.
45. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;**20**: 109–117.
46. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008;**38**:185–190.
47. Van Cauwenberge P, Watelet JB, Van Zele T, Bousquet J, Burney P, Zuberbier T. Spreading excellence in allergy and asthma: the GA²LEN (Global Allergy and Asthma European Network) project. *Allergy* 2005;**60**:858–864.
48. Heinzerling L, Frew AJ, Bindslev-Jensen C, Bonini S, Bousquet J, Bresciani M et al. Standard skin prick testing and sensitization to inhalant allergens across Europe – a survey from the GALEN network. *Allergy* 2005;**60**: 1287–1300.
49. Burney P, Potts J, Kowalski M, Joos G, Godnic-Cvar J, Skadhauge L et al. A case-control study of the relation between plasma selenium in European populations. A GA²LEN project. *Allergy*. 2008;**63**:865–871.
50. Strom B, Klimmel S. Textbook of pharmacoepidemiology. Sussex: John Wiley, 2006.
51. Conforti A, Leone R, Moretti U, Mozzo F, Velo G. Adverse drug reactions related to the use of NSAIDs with a focus on nimesulide: results of spontaneous reporting from a northern Italian area. *Drug Saf* 2001;**24**:1081–1090.
52. Leone R, Conforti A, Venegoni M, Motola D, Moretti U, Meneghelli I et al. Drug-induced anaphylaxis: case/non-case study based on an Italian pharmacovigilance database. *Drug Saf* 2005;**28**:547–556.
53. Sachs B, Fischer-Barth W, Erdmann S, Merk HF, Seebeck J. Anaphylaxis and toxic epidermal necrolysis or Stevens-Johnson syndrome after nonmucosal topical drug application: fact or fiction? *Allergy* 2007;**62**:877–883.
54. Sachs B, Riegel S, Seebeck J, Beier R, Schichler D, Barger A et al. Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Saf* 2006;**29**:1087–1100.
55. Durrieu G, Olivier P, Bagheri H, Montastruc JL. Overview of adverse reactions to nefopam: an analysis of the French pharmacovigilance database. *Fundam Clin Pharmacol* 2007;**21**: 555–558.
56. de Boer HJ, Hagemann U, Bate J, Meyboom RH. Allergic reactions to medicines derived from *Pelargonium* species. *Drug Saf* 2007;**30**:677–680.
57. Holdcroft A. UK drug analysis prints and anaesthetic adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2007;**16**:316–328.