

P. Demoly¹
R. Kropf
A. Bircher
W.J. Pichler¹, for EAACI
interest group on drug
hypersensitivity²

Drug hypersensitivity: questionnaire

Authors' affiliations:

P. Demoly, Maladies Respiratoires – INSERM
U454, Hôpital Arnaud de Villeneuve, University
Hospital of Montpellier, 34295 Montpellier
Cedex 05, France

R. Kropf, W.J. Pichler, Institut für Immunologie
und Allergologie, Inselspital, 3010 Bern,
Switzerland

A. Bircher, Dermatologische Klinik – Allergie,
Kantonsspital, Petersgraben 4, 4031 Basel,
Switzerland

Drug hypersensitivity is a common and complicated problem in clinical practice. The clinical picture of drug hypersensitivity is very heterogeneous, encompassing such distinct diseases as morbilliform or bullous exanthema, urticaria, anaphylaxis, blood cell dyscrasia, fever, interstitial lung disease, hepatitis, nephritis, and various forms of autoimmune diseases. Drug hypersensitivity has taken over the role of the great imitator of diseases from lues in former times. It is an interesting thought that a better understanding of the pathomechanism of drug allergy may even shed some light on the pathomechanism of those diseases imitated by drug hypersensitivity.

The diagnosis of drug hypersensitivity is difficult, and drug-allergic reactions are surely underdiagnosed. This difficulty is related to the following factors:

- 1) the variability of the clinical picture
- 2) insufficient understanding of the pathophysiologic reactions of most drug hypersensitivities
- 3) some weakness of the classification of allergic reactions into four types according to Gell and Coombs, which is

¹ To whom requests for reprints or for e-mailing of the questionnaire can be directed (werner.pichler@insel.ch or demoly@montp.inserm.fr).

² This questionnaire was evaluated within the ENDA (European Network of Drug Allergy, the EAACI interest group on drug hypersensitivity) with the following additional members: Drs W. Aberer, J. Birnbaum, M. Blanca, K. Brockow, T. Fuchs, E. Gomes, J.L. Gueant, C. Guetgesell, H.-J. Hermann, A. Kapp, G. Marone, H. Merk, D. Moneret-Vautrin, C. Pascual-Marcos, B. Przybilla, J. Ring, A. Romano, A. Sabbah, J. Sainte Laudy, D. Vervloet, D. Vieluf, B. Wedi.

Date:

Accepted for publication 17 March 1999

To cite this article:

Demoly P., Kropf R., Bircher A. & Pichler W.J.
Drug hypersensitivity: questionnaire.
Allergy 1999; 54, 999–1003.

Copyright © Munksgaard 1999

ISSN 0105-4538

helpful for some drug-allergic reactions but fails to explain the most common form of drug allergy – exanthema – as well as some severe reactions such as toxic epidermal necrolysis, or the so-called hypersensitivity syndromes

- 4) the limitation and lack of standardization of the available *in vivo* and *in vitro* test procedures to detect drug hypersensitivity reactions.

In view of these difficulties, most doctors restrict themselves to a careful clinical history, reference books (1–3), local agencies monitoring drug hypersensitivity, and/or databanks describing side-effects attributed to a certain drug. However, only a formal diagnosis of drug allergy allows one to bring into play the measures required for prevention and treatment.

Drug hypersensitivity diagnosis is actually split into two parts, which differ between the acute stage and remission. During the *acute stage*, the main question is, whether or not the disease is caused by an allergic/hypersensitivity reaction to a drug. This differential diagnosis should be familiar to any doctor treating patients. A detailed history of previous exposure to and tolerance of the drug incriminated, an exact description of the clinical picture, and an evaluation of enzymes indicating liver or kidney involvement as well as the presence of eosinophilia are important and sometimes sufficient indicators of drug hypersensitivity.

At a later stage, after *remission* of the acute reaction, some patients require further evaluation. Then the allergologist might be asked to find out which of the different drugs taken may have caused the reaction. This can be done by provocation and certain laboratory or skin tests.

A detailed history is of paramount importance for the question of whether a certain disease reflects drug hypersensitivity as well as the question of which drug is causing it. To facilitate this recording of an appropriate history and

to harmonize this procedure in Europe, members of ENDA (European Network of Drug Allergy, which is the interest group on drug hypersensitivity of the EAACI) have developed a questionnaire which might provide a guide in this rather difficult area of clinical medicine. At first sight, this protocol seems to be complicated, but actually it takes only about 5–6 min to complete. The questionnaire is a practical compromise, as it combines questions and investigations important for the *acute* as well as *remission* stage. 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-induced hypersensitivity reactions (blood differential, liver, and kidney parameters). These aspects of the history and the examinations might represent a common denominator of different centers using this protocol.

In addition, the questionnaire contains some special procedures for the diagnosis of drug hypersensitivity, including skin, provocation, and biologic tests, which are applied in certain specialized centers, but are mostly not yet standardized. The application of these procedures (patch testing using different carriers, lymphocyte transformation tests, etc.) in relation to a standardized protocol might help to clarify the relevance of these tests and thus improve both our knowledge and skills in diagnosing drug hypersensitivities, particularly classical allergic reactions.

We hope that this questionnaire will be practically useful and a starting point in the validation of special procedures. On the other hand, we are aware that the different clinics in Europe interested in diagnosis of drug hypersensitivity have a distinct expertise and differ in the acceptance of not yet standardized skin test procedures and access to special laboratory tests. Thus, adaptation of the protocol to their local needs might be required. Further suggestions to improve the protocol are appreciated.

References

1. Bork K. *Kutane Arzneimittelnebenwirkungen*. Stuttgart: Schattauer, 1985.
2. Litt JZ, Pawlak WA. *Drug eruption reference manual*. New York: Parthenon, 1997.
3. Zürcher K, Krebs A. *Cutaneous side effects of systemic drugs*. Basel: Karger, 1992.

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 ☐ FRisk 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:

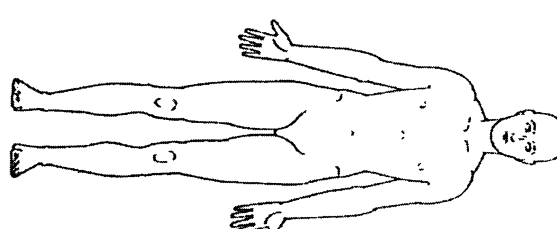
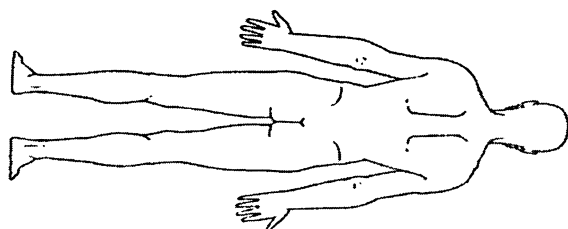
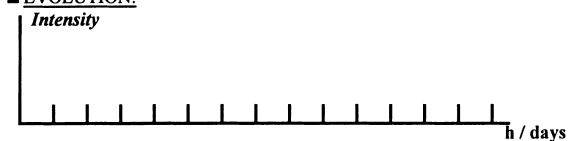
- ☐ Maculopapular exanthema
☐ Macular exanthema
☐ Urticarious exanthema
☐ AGEP (Acute generalized exanthematous pustulosis)
☐ Eczematoid exanthema
☐ Erythema exudativum multiforme
☐ Bullous exanthema
☐ Stevens-Johnson syndrome / TEN (M. Lyell)
☐ Fixed drug exanthema
☐ Purpura -> Thrombocyte count :
 ☐ 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:☐ generalized**GASTROINTESTINAL AND RESPIRATORY SYMPTOMS:**

- ☐ Nausea/Emesis
☐ Diarrhea
☐ Gastrointestinal cramps
☐ Cough
☐ Dysphonia
☐ Dyspnea PEF₁ or FEV₁ :
☐ Wheezing/Bronchospasm

- ☐ Rhinitis
☐ Rhinorrhea
☐ Sneezing
☐ Nasal obstruction
☐ Other/Specification:

PSYCHIC SYMPTOMS:

- ☐ Fear/Panic reaction ☐ Vertigo
☐ Fainting
☐ Paraesthesia/Hyperventilation
☐ Sweating
☐ Other/Specification:

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:

- ☐ Tachycardia Pulse rate:/min
☐ Hypotension Blood pressure: mmHg
☐ Collapse
☐ Arrhythmia
☐ Other/Specification:

INVOLVEMENT OF OTHER ORGANS :

- (e.g. peripheral neuropathy, lung involvement, cytopenia, etc.)
☐
☐
☐

■ **CLINICAL OUTCOME:**

■ List all drugs including Over The Counter substances, natural remedies and additive-containing food taken at the time of the reaction:

■ **SUSPICIOUS DRUGS:**

Drug's generic name ± additives / Indication:	Daily dose / Route of application / Duration of therapy:	Interval between dose and reaction	Previous therapy with this drug:
1.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....
2.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....
3.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....
4.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....
5.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....
6.	mg/d;; d		☐ No ☐ Unknown ☐ Yes -> Symptoms:.....

.....
☐ **CURRENT DRUGS:** ☐ Antihistamines
☐ β-Blockers

■ **MANAGEMENT FOLLOWING ACUTE DRUG REACTION:**

☐ No therapy

- ☐ Stopping suspicious drugs No. #
☐ Antihistamines ☐ local ☐ systemic
☐ Corticosteroids ☐ local ☐ systemic
☐ Bronchodilators ☐ local ☐ systemic
☐ Shock treatment ☐ Epinephrine ☐ Plasma expanders ☐ Other:
☐ Change to substitute/s:
☐ Type/Name:
☐ Tolerance:
☐ Other/Specification:.....
☐ Dosis reduction (Drug.....).
☐ Other/specify.....

PERSONAL HISTORY:

1) HAVE SIMILAR SYMPTOMS BEEN OBSERVED WITHOUT THE INTAKE OF THE SUSPICIOUS DRUGS ? ☐ Yes ☐ No ☐ Unknown

2) **MEDICAL HISTORY:**

- | | | |
|---|---|--|
| ☐ Asthma | ☐ Autoimmune (Sjögren, Lupus, etc.) | ☐ Urticaria pigmentosa / syst. mastocytosis |
| ☐ Nasal polyposis | ☐ Lymphoproliferic (ALL, CLL, Hodgkin, etc.) | ☐ Chronic urticaria |
| ☐ Cystic fibrosis | ☐ Intervertebral disk surgery | ☐ HIV positivity |
| ☐ Diabetes | ☐ Liver:..... | ☐ Kidney: |
| ☐ Other/Specification: | | |

3) **ALLERGIC DISEASES:**
 (e.g. pollinosis, atopic dermatitis, food allergy, Hymenoptera venom allergy, latex allergy, etc.)

4) **DRUG REACTIONS DURING PREVIOUS SURGERY:**☐ Dentist ☐ Local anaesthesia ☐ General anaesthesia (No:.....)

5) **REACTIONS DURING PREVIOUS VACCINATIONS:**☐ Polio ☐ Tetanus ☐ Rubella ☐ Measles ☐ Hepatitis B
☐ Diphtheria ☐ Other:..... ☐ Unknown

FAMILY HISTORY: Allergies / Drug allergies:

REMARKS:

DIAGNOSTIC PROCEDURES:

■ ACUTE DIAGNOSTICS: (already performed)		DATE	NORMAL	ABNORMAL	QUESTIONABLE
☐ Blood:	☐ Full blood count: ☐ Eosinophils:		☐	☐ Value:.....rel.; abs.	☐
	☐ Other:.....		☐	☐ Value:.....rel.; abs.	☐
	☐ ECP (Eosinophil cationic protein)		☐	☐ Value:.....	☐
	☐ C-reactive protein / Erythrocyte sedimentation rate		☐	☐ Value:.....	☐
	☐ Flowcytometry (Specify:)		☐	☐	☐
	☐ Tryptase		☐	☐ Value:.....	☐
☐ Liver parameters:	☐ GOT		☐	☐ Value:.....	☐
	☐ GPT		☐	☐ Value:.....	☐
	☐ γGT		☐	☐ Value:.....	☐
	☐ alk. Phosphatase		☐	☐ Value:.....	☐
☐ Kidney:	☐ Creatinine		☐	☐ Value:.....	☐
	☐ Methylhistamine		☐	☐ Value:.....	☐
	☐ Other:.....		☐	☐	☐
☐ Special:	☐ Mediators and metabolites (IL-4, IL-5, IL-10, IFNγ)		☐	☐ Value:.....	☐
	☐ Immune complex analysis		☐	☐	☐
	☐ Complement analysis		☐	☐	☐
	☐ Skin biopsy:				

■ DIAGNOSTICS:

		NEGATIVE	POSITIVE	QUESTIONABLE
<u>Skin tests:</u>	☐ Prick :	☐	☐ Immediate-R. ☐ Late-R.	☐
		☐	☐ Immediate-R. ☐ Late-R.	☐
		☐	☐ Immediate-R. ☐ Late-R.	☐
	☐ Intradermal:	☐	☐ Immediate-R. ☐ Late-R.	☐
		☐	☐ Immediate-R. ☐ Late-R.	☐
	☐ Scratch-Patch:	☐	☐ Immediate-R. ☐ Late-R.	☐
		☐	☐ Immediate-R. ☐ Late-R.	☐
		☐	☐ Immediate-R. ☐ Late-R.	☐
	☐ Other:	☐	☐ Immediate-R. ☐ Late-R.	☐

Blood analysis:

☐ Total IgE	☐ Value:.....
☐ Specific IgE for drugs: ☐ CAP ☐ RAST	☐ Value:.....
.....	☐ Value:.....
.....	☐ Value:.....
.....	☐ Value:.....
☐ Specific IgG/Coombs Test dir:	
☐ Coombs test indir.	
☐ Other:.....	

Cellular tests:

☐ Lymphocyte transformation test (LTT):.....	☐	☐ SI:.....	☐
.....	☐	☐ SI:.....	☐
.....	☐	☐ SI:.....	☐
☐ Basophil activation test (Specify:)	☐	☐	
☐ CAST assay	☐	☐	☐
☐ Other:.....	☐	☐	

Provocation tests:

☐ Local anaesthetics:.....	☐	☐
☐ NSAID:.....	☐	☐
.....	☐	☐
☐ Aspirin	☐	☐
☐ Paracetamol	☐	☐
☐ Nimesulid	☐	☐
☐ β-lactam antibiotics:.....	☐	☐
.....	☐	☐
☐ Other:.....	☐	☐

CONCLUDING INTERPRETATION:

☐ Type I reaction (IgE mediated)	to: A.....
☐ Type II reaction (antibody mediated)	to: B.....
☐ Type III reaction (immune complexe mediated)	to: C.....
☐ Type IV reaction (cell-mediated, late-type reaction)	to: D.....
☐ Cytotoxic reaction, cell-mediated	to: E.....
☐ Pseudoallergic reaction	to: F.....
☐ Pharmacological reaction	to: G.....
☐ Psychophysiological reaction	to: H.....
☐ Other:.....	to: I.....

■ PROBABILITY SCALE CONCERNING THE CAUSAL RELATIONSHIP BETWEEN DRUG & REACTION:

(Please mark the drug's letter on the scale)

Certain	Probable	Possible	Doubtful	Unrelated / Not assessible

Please specify:

☐ DECLARATION TO REGULATORY AGENCY ? : ☐ No ☐ Yes ☐ To whom ? : Date:**REMARKS:**.....

.....