Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE ANAPHYLAXIS

Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010

J.-M. Renaudin[1,2], E. Beaudouin[1,2], C. Ponvert[2,3], P. Demoly[2,4] & D.-A. Moneret-Vautrin[1,2]

[1]Department of Allergy, E Durkheim Hospital, Epinal; [2]Allergy Vigilance Network, Vandoeuvre les Nancy; [3]Department of Pediatrics, Pulmonology, Allergy and Dermatology, Sick Children's Hospital, Paris; [4]Allergy Department, Inserm U657, Hôpital Arnaud de Villeneuve, Montpellier University Hospital, Montpellier, France

To cite this article: Renaudin J-M, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin D-A. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy* 2013; **68**: 929–937.

Keywords
drug anaphylaxis; IgEs; oral challenge; skin tests.

Correspondence
D.-A. Moneret-Vautrin, Allergy Department, E Durkheim Hospital, 3 Avenue Robert Schuman, 88000 Epinal, France.
Tel.: 03 83 67 82 69
Fax: 03 83 67 89 99
E-mail: reseau@allergyvigilance.org

Accepted for publication 8 March 2013

DOI:10.1111/all.12168

Edited by: Thomas Bieber

Abstract

Background: A few series of well-documented cases of severe drug-induced anaphylaxis (SDA) are available.
Methods: Cases collected by the Allergy Vigilance Network from 2002 to 2010 were analyzed for clinical signs, causative drugs, and efficacy of a stepwise approach to diagnosis, using skin tests, laboratory tests, and oral challenges.
Results: Three hundred and thirty-three cases concerned 300 adults (90.1%) and 33 children (9.9%): 206 females (61.9%) and 127 males (38.1%). Mean age was 42.7 ± 18 years. Anaphylactic shock (76.6%), severe systemic reactions (10.5%), acute laryngeal edema (9%), severe bronchospasm (2.1%), and six fatal cases (1.8%) were recorded. There were 270 cases (81.1%) of ambulatory anaphylaxis. Sixty-three cases (18.9%) occurred during anesthesia. Hospitalization was required in 94.8% of cases. 23.7% of patients were admitted to an intensive care unit. Epinephrine was used in 57.9% of cases. Eighty-four drugs were incriminated: antibiotics (49.6%), muscle relaxants, latex and anesthetics (15%), nonsteroidal anti-inflammatory drugs (10.2%), acetaminophen (3.9%), iodinated or magnetic resonance imaging contrast media (4.2%), immunotherapy and vaccines (3.9%), and other drugs (13%). Among antibiotics, amoxicillin (97 cases), other penicillins (four cases), cephalosporins (41 cases), quinolones (15 cases), and pristinamycin (seven cases) were the most common. The diagnosis of drug hypersensitivity was obtained by skin tests in 72.9%, laboratory tests only in 2.4% of cases, and oral challenges (OCs) only in 3.9% of cases.
Conclusions: Three hundred and thirty-three case reports provided data on drugs involved in severe anaphylaxis. The efficacy of skin tests and poor use of laboratory tests are underlined. Further progress may depend on OCs.

Adverse drug reactions (ADRs) are a major public health problem. The overall incidence of ADRs among hospitalized patients has been estimated between 6% and 15% (1–3). Anaphylaxis is defined as a life-threatening reaction resulting from mast cell derived mediator release (4). The incidence in Europe and the United States has been estimated from 3 to 300 per 100 000 persons per year (5). Severe anaphylaxis is estimated to cause death in 0.6–2% of patients (5–7). Drugs are one of the main identified causes of anaphylactic shock (AS) (5, 8). All routes of administration are potentially fatal (6). Anaphylaxis guidelines suggest specific management with instructions to avoid the incriminated drug and referral to an allergy specialist (10). Yet, drug anaphylaxis is rarely documented by allergy tests, which might provide more information and thus prevent further reactions (10).

We report 333 cases declared by the Allergy Vigilance Network© from 2002 to 2010, documenting incriminated drugs, clinical symptoms, and chronology. We show the efficacy of skin tests and the poor use of laboratory tests and oral challenges (OCs). Moreover, these data confirm the need for OCs to assess ADRs induced by Nonsteroidal anti-inflammatory drugs (NSAIDs).

Materials and methods

Case collection

The Allergy Vigilance Network© was set up in 2001 to record severe anaphylactic reactions (11). Data from trained allergists were collected by e-mail in a standardized form including sex, age, clinical features, chronology of symptoms, emergency treatment administered, possible risk factors of anaphylaxis, any associated medication, and the results of allergy testing. Cases were validated by the coordinators.

Anaphylaxis was defined according to the criteria proposed at the second anaphylaxis symposium (4). These criteria include immediate onset of a serious reaction after exposure to a drug, systemic symptoms affecting two or more organs and/or systems (i.e., crampy abdominal pain, reduced blood pressure or collapse, syncope, involvement of skin, mucosal tissue, respiratory system), and the need for emergency care. Severity was evaluated according to Ring's classification (12).

Case reports were then classified into five categories: AS, involving several organs and loss of blood pressure, severe systemic reaction (SSR), involving several organs but without cardiovascular collapse, suffocating laryngeal angioedema (LAO), severe bronchospasm (SB), and death (D).

Assessment of drug allergy

After a detailed clinical history, drug allergy assessment used a three-step procedure to establish immediate hypersensitivity to drugs: skin prick tests (SPTs, first line) and then intradermal tests (IDTs, second line) (13–16). *In vitro* tests were carried out mostly when skin tests were positive and sometimes when they were negative. Oral challenge tests were performed in hospital settings when skin tests and *in vitro* tests were negative or when there were several associated drugs. This procedure has been proposed earlier (17, 18). Finally, this stepwise approach was scrutinized to clarify the optimal restrictive use of OC.

Skin test procedures followed European network for drug allergy, the EAACI drug allergy interest group (ENDA/EAACI) criteria (13). Concentrations have been validated for beta-lactam antibiotics and muscle relaxants (14, 15) and published for iodinated contrast media (ICM) in a large series of patients (19). For non injectable drugs, the prick test was performed using powder.

Specific IgE assays (Phadia) were carried out when available. Leukocyte histamine release tests or basophil activation tests (BATs; detection of CD63 or CD103c by flow cytometry) were performed by specialized biology units for amoxicillin, cefuroxime, acetaminophen, diclofenac, ketoprofen, gadolinium contrast media (CM), human insulin, *Viscum album*, horse chestnut extract, and framycetin.

In certain cases, OCs were performed with the associated drugs, and not with the most suspected one, to check that they were tolerated, thus restricting causality to the suspected drug. Other OCs were performed predictively to authorize later use.

When allergy tests were negative or had not been performed (9), methods from the pharmacovigilance system were used to assess plausible drug allergy and were based on intrinsic, patient-related, and extrinsic, literature-related criteria.

Results

Fifty-nine allergists reported 333 cases of severe drug-induced anaphylaxis from 2002 to 2010. There were 206 females (61.9%) and 127 males (38.1%), 300 adults (mean age = 46.4 ± 14.6 years), and 33 children (mean age = 9.8 ± 4.5 years). The mean age was 42.7 ± 18 years (1–85 years). There were 255 cases of AS (76.6%), 35 cases of SSRs (10.5%), 30 cases of suffocating LAO (9%), and seven cases of severe bronchospasm (2.1%). There was one case of biphasic anaphylaxis and two cases of multiple drug allergy syndrome. Six deaths (1.8%) were linked to injections of the following drugs: suxamethonium (2), amoxicillin (2) (one occurred in the fetus), hydroxycobalamin (1), and *per os* intake of an angiotensin-converting enzyme inhibitor (1).

Two hundred and fifty-six patients (94.8%) were hospitalized in emergency departments, and 65 of 256 (21.7%) were directly admitted to intensive care units. In 63 cases (18.9%), the incriminated drug had been infused during general anesthetic (47 females [74.6%] and 16 males [25.3%]). Epinephrine was used in 57.9% of cases.

Associated drugs, being potential risk factors enhancing the severity of anaphylaxis, were recorded for 47 cases (14.1%): β-blockers (11 cases, 3.3%), angiotensin-converting enzyme (ACE) inhibitors (10 cases, 3%), angiotensin II receptor antagonists (ARA, four cases, 1.2%), NSAIDs or aspirin (eight cases, 2.4%), and an association of β-blockers with ACE inhibitors or ARAs (nine cases, 2.7%). Other triggering factors were exercise (two cases, 0.6%) and alcohol (two cases, 0.6%).

The incriminated drug was administered by the oral route (58.5%), intravenous route (28.8%), subcutaneous route (5.7%), intramuscular route (2.4%), skin application (4.2%), and intra-articular administration in one case. Time to onset of anaphylactic reaction was 28 min for oral intake (32 min for aspirin and NSAIDs), 7 min for intravenous infusion, 10 min for intramuscular injection, 16 min for subcutaneous injection, and 29 min for skin application.

Incriminated drugs

Eighty-four different drugs were incriminated. Antibiotics were involved in 165 cases (49.6%) (Table 1): beta-lactams (138 cases), quinolones (15 cases), pristinamycin (seven cases), and other antibiotics (five cases). Details of beta-lactam antibiotics are as follows: amoxicillin (97 cases, 29.1%), methyl penicillin (1), bacampicillin (1), piperacillin (2), and cephalosporins (41 cases, 12.3%) that includes the following: cefuroxime (15), ceftriaxone (7), cefoxitin (1), cefadroxil (2) cefaclor (4), cefatrizine (6), cefamandole (2) cefazolin (1), cefpodoxime (2), and cefixime (1). The second group was quinolones with moxifloxacin (eight cases), ofloxacin (3), lomefloxacin (2), norfloxacin (1), and flumequine (1), respectively. The other antibiotics or antiparasitic drugs were

Table 1 Efficiency of skin tests, biology, and oral challenges, respectively, for the diagnosis of anaphylaxis to antibiotics

		IgE-dependent allergy confirmed					Plausible drug allergy
Antibiotics (ATB)	Cases (n)	Positive prick test (%)	Negative prick test and positive ID test (%)	Negative PT and IDT and positive *in vitro* tests (%)	Negative allergy testing and positive oral challenge (immediate reaction) (%)	Clinical criteria: symptoms, chronology, and single drug (%)
Amoxicillin and other penicillins	97	50	40.5	6.3	1	2.2
Cephalosporins	41	58.5	24.4	4.9	0	12.2
Quinolones	15	46.7	13.3	0	0	40
Other ATB	12	50	8.3	8.3	0	33.4

pristinamycin (seven cases), framycetin (1), minocycline (1) fosfomycin (1), vancomycin (1), and proguanil (1).

Muscle relaxants were reported 36 times (Table 2): suxamethonium (18 cases), atracurium (8), cisatracurium (5), rocuronium (4), and mivacurium (1). Latex allergy was diagnosed in six cases. Other drugs were ketamine (two cases), propofol (1), sufentanil (1), morphine (1), gelatin (2), procaine (1), and lidocaine (1).

Anaphylactic reactions to CM were reported in 14 cases: gadolinium-based CM in nine cases and iodinated CM in five cases (Table 4). Subcutaneous immunotherapy to venom, dust mites and grass pollens, and vaccines were incriminated in 13 cases (3.9%). Nonsteroidal anti-inflammatory drugs and aspirin were involved in 33 cases (9.9%) and acetaminophen in 13 cases (3.9%) (Table 3). Other drugs were also implicated (Table 4).

Skin tests

Skin testing was performed in 302 of 333 patients (90.6%): SPTs: 194 and IDTs: 176 (Tables 1–3). Tests were positive in 80.5% of cases: SPTs: 99 (51%); IDTs: 148 (84%). A moderate systemic reaction was induced in six cases (1.8%). The efficacy of prick tests was 50% for amoxicillin and penicillins, 58.5% for cephalosporins, and 70% for other antibiotics. When SPTs were negative, IDTs were positive in 39.3% for penicillins, 24.4% for cephalosporins, and 5% for other antibiotics. For muscle relaxants, 48.7% of prick tests were positive and 35.9% for further IDTs. IgE anaphylaxis to NSAID was established by prick tests in 17.9% of cases. Positive prick tests to gadolinium and ICM were, respectively, four of nine and four of seven cases (Tables 1–3).

In vitro tests

Laboratory tests were performed for 118 patients: 94 specific IgE assays (sIgE assays) and 24 BATs or leukocyte histamine release tests (LHRTs) (Tables 1–4). Specific IgE assays were positive in 67% of cases: succinyl choline or muscle relaxant (24), amoxicilloyl (23), ceftriaxone (1), human insulin (1), tetanus anatoxin (1) for drugs and latex (6), bee venom (3), wasp venom (1), house dust mites (2), and grass pollens (1).

Leukocyte histamine release tests or BATs were positive in 66.6% of cases: amoxicillin (6), suxamethonium (4), atracurium (2) diclofenac (2), acetaminophen (2), gadolinium (2), cefuroxime (1), ketoprofen (1), human insulin (1), *viscum album* (1), horse chestnut (1), fosfomycin (1), enoxaparin (1), and framycetin (1).

Oral challenge tests

Seventy-three double- or single-blind placebo-controlled challenge tests were monitored in 55 patients. Drugs were as follows: acetaminophen (10), aspirin (4), NSAIDs (12), penicillins (12), cefpodoxime (7), ceftriaxone (6), cefuroxime (3), cefixime (2), cefotaxime (1), cefaclor (1), ciprofloxacin (1), gentamicin (1), clarithromycin (1), and other drugs (8).

A single drug was suspected in 39 patients. Thirteen of 15 OCs were positive (acetaminophen: 5, cephalosporin: 3,

Table 2 Efficiency of skin tests, biology, and oral challenge, respectively, for the diagnosis of anaphylaxis to muscle relaxants, latex, anesthetics, perioperative drugs, and contrast media

		IgE-dependent allergy confirmed		
	Cases (n)	Positive prick test	Negative prick test and positive ID test	Negative skin tests and positive *in vitro* tests
Muscle relaxants and latex	42	48.7%	35.9%	15.4%
Anesthetics				
Ketamine	2	0	2 : 5 μg/ml, 5 mg/ml	nd
Morphine	2	0	2 : 10 μg/ml	nd
Sufentanil	1	1 : 5 μg/ml	nd	nd
Gelatins	2	1	1 (10^{-3})	nd
Profofol	1	0	0	1
Total of anesthetics	8	25%	62.5%	12.5%
Gadolinium-based contrast media	9	2	2	4 (BAT, LHRT)
Iodinated contrast media	7	1	3	nd

BAT, basophil activation test; LHRT, leucocyte histamine release test.

Table 3 Diagnosis of adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (33 cases) and acetaminophen (13 cases)

		Nonimmune hypersensitivity		IgE-dependent anaphylaxis			
NSAID	*n*	Clinical criteria: past history of reactions to different NSAIDs and no associated drug	Oral challenge compatible with hypersensitivity	Positive skin tests or BAT	Plausible (past history with the same drug and no intolerance to other NSAIDs) Immediate reaction to low dose	Mechanism unknown (no past history)	Uncertain causality
Diclofenac	4	–	–	2: IDT+BAT	2		
Ketoprofen	5	1	–	1 BAT, 1 PT		2	
Ibuprofen	11	3	1 : 143 mg	1 IDT	1	4	1
Naproxen	1	–	–			1	
Aspirin	5	3	1 : 200 mg			1	
Niflumic acid	1	–	1 : 250 mg			–	
Piroxicam	1	–	1 : 20 mg				
Nabumetone	1	–	–		Labial test: systemic reaction		
Tiaprofenic acid	2	2	–				
Celecoxib	2	–	–			2	
Total NSAIDs (33)		27.3%	12.1%	15.1%	12.1%	30.3%	3%
Acetaminophen	13	0	3	3 PT, 2 BAT	1	4	0
			23%	38.4%	7.8%	30.8%	

IDT, intradermal test; BAT, basophil activation test; PT, prick test.

ibuprofen: 1, aspirin: 2, amoxicillin: 1, macrogol: 1). Allergy to ceftazidime was excluded because of negative OC. Thirty-eight OCs were carried out to provide safe alternatives (mostly 3G cephalosporins), and 35 of 38 were negative.

Two associated drugs were suspected in 16 patients. Seventeen OCs and one SC injection were carried out with the less plausible drug according to the pharmacovigilance system, and 17 cases were negative. In 11 of the 16 patients, the diagnosis of anaphylaxis to the other drug was confirmed by positive SPTs. In five of 16 patients, anaphylaxis was plausible (two cases). Nonimmune hypersensitivity was the final diagnosis in two cases and one case linked to the association of amoxicillin and ibuprofen could not be confirmed by two OCs. In 19 cases of severe anaphylaxis with positive OC, only one case required epinephrine (case 4, Table 5).

Drug assessment

Drug allergy could be diagnosed by prick tests in 72.9% of cases (Fig. 1). When prick tests were negative (59 cases) or not performed (31 cases), laboratory tests were positive in eight of 14 cases, confirming the diagnosis in 4.2% of cases. When laboratory tests were not performed or were negative (82 cases), OC was performed in 29 cases. Thirteen OCs were

Table 4 Other drugs implicated in severe drug anaphylaxis

Drugs	n	Positive skin test	Positive *in vitro* test	Positive oral challenge
Benfluorex	2	nd	nd	nd
Calciparine®	1	+IDT (10^{-3})	nd	nd
Carboxymethylcellulose	2	+	+LHRT	nd
Chloramine T	2	+PT	+CAP (1)	nd
Clavulanic acid	1	+IDT*	nd	nd
Clobutinol	1	+PT	nd	nd
Chlorhexidine	1	+PT 5 mg/ml	nd	nd
Dexchlorpheniramine	1	+IDT 500 μg/ml	nd	nd
Hydroxocobalamine	1 death	nd	nd	nd
Enoxaparine	1	IDT neg	+BAT	nd
Fluoresceine	1	+PT 100 mg/ml	nd	nd
Helicidine®	1	+PT	+(CAP to snail)	nd
Horse chestnut extract	1	Neg	+LHRT	nd
Insulin	2	+IDT (2)	+ CAP (2)	nd
Lisinopril	1 death	nd	nd	nd
Macrogol	2	+PT	nd	nd
		neg		+10 g
Methylprednisolone	2	+IDT 10 μg/ml		+bethametasone
		+IDT 8 mg/ml	nd	
Noramidopyrine	1	+ PT 400 μg/ml	nd	nd
Omeprazole	1	+ PT	nd	nd
Ondansetron	2	+IDT 20 μg/ml	nd	nd
		+IDT 2 mg/ml	nd	nd
Ortho-phthalaldehyde	1	+PT 550 μg/ml	+ BAT	nd
Patent Blue V	2	+PT (10^{-2})	nd	nd
Perindopril arginine–indapamide	1	nd	nd	nd
Pholcodine	3	+PT (3)	+CAP (1): 54 kU/L	nd
			+ BAT (1)	
Phloroglucinol	1	+PT 10^{-2} (AS)	nd	nd
Protamine	1	+IDT 3.5 μg/ml	+BAT	nd
Ranitidine	1	+IDT 250 μg/ml	nd	nd
Séné	1	+PT	nd	nd
Tetanus anatoxin	1	+IDT 10^{-1} (1)	+CAP	nd
Viscum album extract	1	+IDT 30 μg/ml	+BAT and LHRT	nd
Zolmitriptan	1	+PT	nd	nd

CAP, immunoCAP Phadia; IDT, intradermal test; BAT, basophil activation test; PT, prick test; LHRT, leucocyte histamine release test.
*Plausible allergy to clavulanic acid on the basis of positive IDT to amoxicillin–clavulanic acid (25 mg/ml) and negative IDT to amoxicillin.

positive (44.8% of cases). They established the diagnosis of drug hypersensitivity in 3.9% of cases. Finally, the diagnosis of drug allergy or hypersensitivity could be established in 79.2% of cases.

Discussion

Anaphylaxis is under-reported in the French pharmacovigilance system (9). The aim of the Allergy Vigilance Network is to report the cases of severe anaphylaxis from allergists trained to diagnose drug allergy. Most cases benefit from skin testing. The high incidence of positive prick tests may highlight several biases. Maybe allergists did not report cases with negative SPTs because they were not sure of diagnosis. On the other hand, the specificity of prick tests to various drugs cannot be ascertained, as often the quantity is unknown when powder is used, and there were no series of controls, except for muscle relaxants, beta-lactam antibiotics, ICM, and only small series of controls for heparin, insulin, corticosteroids, Patent Blue V, ranitidine, ondansetron, and carboxymethylcellulose.

This series of 333 cases provides further knowledge of the clinical characteristics of SDA and contributes to evaluating the efficacy of a stepwise approach using first SPTs then *in vitro* tests and then discussing the need for OCs as a third step (16, 17).

Eighty-four drugs were involved. In line with previously published data, antibiotics (49.6%), particularly β-lactam antibiotics (41.4%), are the most frequently incriminated drugs (18, 20–22). Anaphylaxis to muscle relaxants is also common (23). Anaphylaxis to gadolinium derivatives is a rising problem (24, 25). The usefulness of SPTs and *in vitro* tests is shown in this series of nine cases. The paucity of cases of ADRs to ICM (five cases) is not explained. It might point to the fact that allergy testing is positive only in 28–50% of cases and even less when the patient is referred

Table 5 Positive oral challenges to drugs in 19 cases of grade 3–4 anaphylaxis

Cases	Sex	Age	Symptoms	Drug	Reactive dose	Onset	Management	Skin tests	OC/CRD	Predictive OC
1	F	54	AS	Acetaminophen, p.o	500 mg	3 h	H, CS, Anti H1	nd	Pos: 500 mg	
2	F	17	AS	Acetaminophen, p.o	500 mg	np	H, np	Neg	Pos: 6 mg	
3	F	48	SSR	Acetaminophen, p.o	500 mg	15 min	H, Epi	Neg	Pos: 144 mg	
4	F	24	AS	Acetaminophen, p.o	500 mg	Np	CS, Anti H1	Pos	Pos: 500 mg	
5	H	8	AS	Acetaminophen, p.o	250 mg	15 min	H, CS	Neg	Pos: 556 mg (grade 2 AS)	
6	H	38	LAO	Aspirin, p.o	500 mg	np	H, Epi	nd	Pos: np	
7	F	5	U, AO	Aspirin, p.o	250 mg	np	CS, anti H1	nd	Pos: 47.5 mg	
8	H	36	SSR	Niflumic acid, p.o	250 mg	30 min	H, Epi, CS, Anti H1	nd	Pos: 250 mg	
9	F	8	SSR	Ibuprofen, p.o	255 mg	2 h	H, CS, anti H1	nd	Pos: 143 mg	
10	F	34	U	Macrogol (PEG 4000) p.o	10 g	1 h	CS, Anti H1,	Neg	Pos: 10 g	
11	F	39	AS	Amoxicillin, ibuprofen, p.o	np	np	H, CS, Anti H1	Neg	Pos: amoxicillin Neg: ibuprofen	
12	H	54	AS	Cefaclor, acetaminophen, p.o	np	np	H, CS, anti H1	Neg	Pos: cefaclor Neg: acetaminophen	
13	F	40	AS	Ciprofloxacine, acetyl cysteine, p.o	400 mg	np	H, Epi, CS	IDT ciprofloxacine 10^{-1}: 7.5 mm PT mucomyst: 4 mm	Pos: ciprofloxacine 8 mg Neg : acetyl cysteine 200 mg	
14	F	27	AS	Amoxicillin, p.o	1 g	15 min	H, CS	Neg	Pos: amoxicillin 144 mg	Neg: ceftriaxone 1440 mg
15	H	5	U	Cefpodoxime, p.o	np	np	H, anti H1	Neg	Pos: cefpodoxime	Neg: amoxicillin Neg: IV ceftriaxone
16	F	5	LAO, U	Cefpodoxime, p.o	np	np	np	Neg	Pos: cefpodoxime, doses repeated every day during 7 days Neg: amoxicilline	Pos: ceftriaxone
17	F	7	AS	Ibuprofen, p.o	200 mg	np	H, Epi	Neg	Pos: aspirin 200 mg	
18	F	29	SSR	Ibuprofen, p.o	np	np	H, CS, anti H1	nd	Pos: piroxicam 20 mg	Neg: rofecoxib
19	F	27	AS	IV Methylprednisolone	np	<5 min	np	IDT 0.01 mg/ml: + IDT betamethasone 4 mg/ml: neg	Pos: betamethasone 1.25 mg	

AS, Anaphylactic shock; IDT, intradermal tests; SSR, serious systemic reaction; U, generalised urticaria; LAO, laryngeal angioedema; AO, angioedema; p.o, per os; SC, subcutaneous; np, not precised; nd, not done; H, hospitalization; CS, IV corticosteroids; OC, oral challenge; CRD, cumulated reactive dose; DBPCOC, double-blind placebo-controlled oral challenge; Epi, epinephrine; neg, negative; pos, positive.

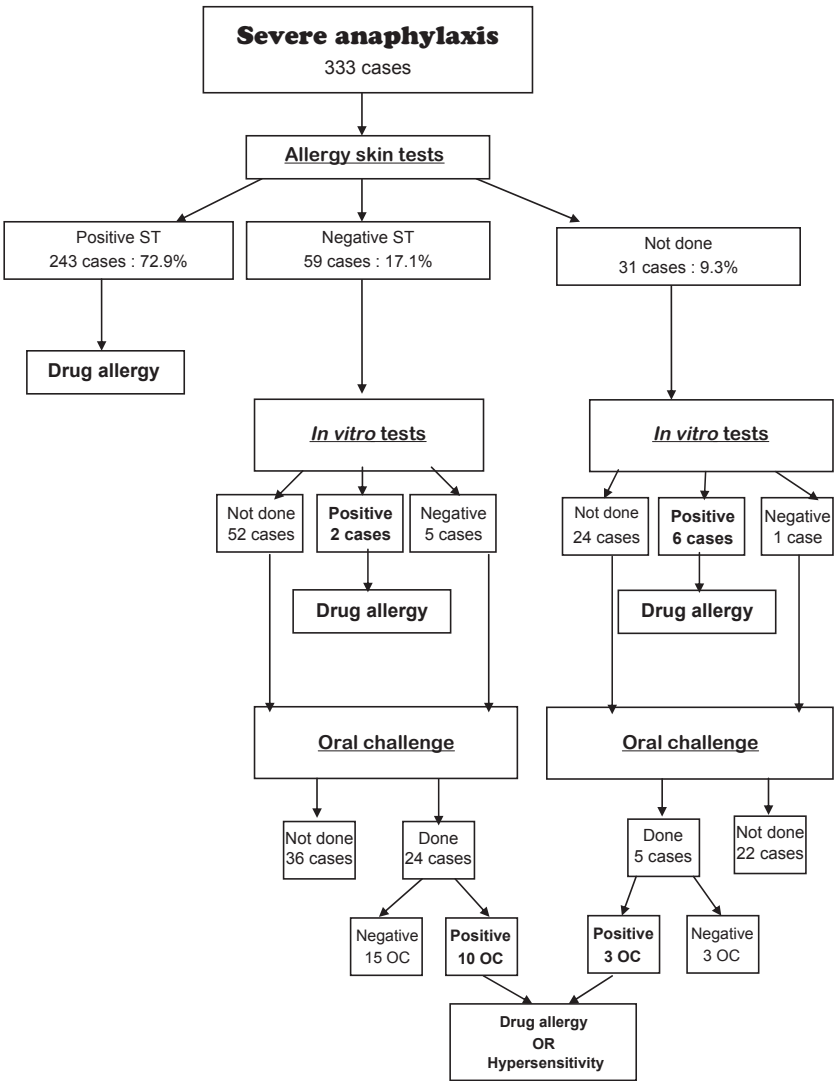

Figure 1 Evaluation of the stepwise approach of diagnosis of drug anaphylaxis through data obtained in 333 cases.

more than 6 months after the reaction (26, 27). Cases of exceptional drug allergies were detected mainly by SPTs completed by IDTs.

The diagnosis of ADRs to NSAID is a challenging problem, as they involve two mechanisms: nonimmune ADR or nonimmune hypersensitivity and IgE-dependent anaphylaxis (28, 29). Nonimmune hypersensitivity may be alleged when there is past history of ADR to other NSAIDs and time to onset of ADR longer than 45 min (28, 29). IgE-dependent anaphylaxis can be established by prick tests and *in vitro* tests. A positive OC may suggest either mechanism. This series documents the relative incidence of these mechanisms. IgE-dependent anaphylaxis is plausible when the eliciting dose is low and the onset of the reaction immediate. The diagnosis of ADRs to NSAIDs was nonimmune hypersensitivity on the account of past history of reactions to other NSAIDs in nine cases (27.3%) and based on positive OC in four cases (12.1%). IgE-dependent anaphylaxis was established by prick tests in five cases (15.1%) and alleged in four cases (12.1%) on the basis of an immediate onset, a low eliciting dose, and no hypersensitivity to other NSAIDs. The mechanism remained unknown in 10 cases (30.3%). Uncertain causality was quoted in one case (3%) (Table 3).

Diclofenac may be a major cause of IgE-dependent anaphylaxis (30–32). In this series, four of four cases were IgE-dependent anaphylaxis (Table 3). A total of 23% of ADRs to acetaminophen may be related to nonimmune hypersensitivity and 46.2% to IgE-dependent anaphylaxis. The mechanism remains unknown in 30.8% of cases (Table 3). Systematic OCs deserve consideration. Such a procedure provided 13.4%–50% of positive challenges in previous studies (33, 34).

We examined how many cases would have been diagnosed by a stepwise approach. The first step was SPTs, and the relevance of laboratory tests was scrutinized only when they were performed as a second step, if SPTs were negative or

not performed. Oral challenges should be carried out as a third step only when previous tests were negative or not performed.

Drug allergy was diagnosed by prick tests in 72.9% of cases (Fig. 1). The second step of laboratory tests concerned only 14 cases and detected 2.4% more cases. The fact that eight of 14 laboratory tests were positive indicates that they should be used more often. When prick tests and laboratory tests were negative or not performed, 44.8% of OCs (of 29 cases) were positive, supporting current recommendations for use of OC as emphasized by the EAACI/GA2LEN group (28).

When anaphylaxis is suspected on account of AS, SSR, and LAO, there is no consensus about the use of OC. This series shows that a systemic reaction to OC occurred in only in one of 19 cases. The benefit–risk ratio of OC has to be carefully weighed in anaphylactic patients. Indications, contraindications, and adequate methods for performing OCs have been published and should be followed (17). OCs must always be carried out in hospital settings by trained allergists and with incremental doses.

Conclusion

The data issuing from this series of patients over 9 years underline the accuracy of information displayed by allergists' reports and based on a common methodology of diagnosis. Epidemiological data were analyzed by the Allergy Vigilance Network. The results obtained for SPTs, *in vitro* tests, and OCs have to be considered together with classical criteria of causality (chronology, semeiology, and the literature review) used by the European Pharmacovigilance system. Analysis of this series provides data on the etiology of drug anaphylaxis and underlines the benefit of allergy assessment using a three-step procedure for optimal diagnostic approach.

Acknowledgments

The authors thank the members of Allergy Vigilance Network who have reported cases of severe drug anaphylaxis with drug allergy assessment: A Andrier Schmitt (Thonon les Bains), A Auffret (Angers), E Beaudouin (Epinal), I Begon Bagdassarian (Paris), V Bertrac (Rennes), B Bilo (Rome), A Blanchard (Montluçon) M Boulegue (Brive la Gaillarde), I Bossé (La Rochelle), F Bord (Périgueux), M Buard (Rennes), P Chalmet (Montluçon), C Chappard (St Etienne), MP Chataignault (Poitiers), A Cheynel (Chambéry), F Codreanu (Nancy), V Cordebar (Nancy), A Croizier (Nancy), JJ Crognier (Rodez), C Debavelaere (Boulogne sur Mer), F De Blay (Strasbourg), MF Defrance Hutinet (Verrières Le Buisson), S Delauney (Nouméa), F Delepoulle (Dunkerque), P Demoly (Montpellier), JM Devoisins (Cholet), M Dona (Paris), M Dron Gonzalves (Martigues), B Dubegny (Laval), P Dumond (Nancy), Y El Guedarri (Maroc), M Epstein (Paris), MF Fardeaux (Aix en Provence), C Gallen (Narbonne), J Gayraud (Tarbes), L Guenard Bilbaut (Strasbourg), JL Grand (Belgium), JL Hallet (Luneville), C Hanss (Metz), N Herpin Richard (Le Chesnay), JP Jacquier (Chambéry), G Kanny (Nancy), S Khouader (Paris), C Langlet (Bayonne), MP Larchevesque-Perimony (Rouen), F Leprince (Saint Quentin), J Lesellin (Angers), F Louis Donguy (Nice), S Lyasu (Arlon), JP Mallet (Saint-Nazaire), C Marty Enguehard (Saint-Nazaire), F Malauzat (Olivet), H Masson (Bordeaux), JP Meyer (Dôle), P Mols (Belgium) DA Moneret-Vautrin (Nancy), C Morel-Rochefort (Rennes), M Morisset (Nancy), C Mouton (Nancy), C Nootens (Belgium), B Omarjee (La Réunion), O Outas (Clermont-Ferrand), ML Paquin (Pontarlier), C Pasquet Noualhaguet (Bois d'Arcy), A Pipet (Nantes), JG Petit (Angoulême), N Petit (Nancy), F Pirson (Belgium), C Ponvert (Paris), E Puillandre (Arcachon), JM Renaudin (Epinal), D Sabouraud (Reims), J Sainte Laudy (Limoges), E Schneider (Belgium), A Sorlin (Berck Sur Mer), JM Rame (Besançon), R Stenger (Obernai), I Sullerot (Sens), P Terrier (Le Havre), X Van Der Brempt (Belgium), S Widmer (Nancy), and H Zana (Belfort). We are grateful to Mrs S Tscheiller, analyst for the Allergy Vigilance Network, for her technical assistance.

Author contributions

J. M. Renaudin contributed to the analysis of the data from 333 cases recorded by the Allergy Vigilance Network and writing of the manuscript; E. Beaudouin contributed to declared cases with standardized OCs in hospital settings; C. Ponvert contributed to declared cases with standardized OCs in hospital settings and also to the revision of the manuscript; P. Demoly involved in the scientific contribution to the study and revision of the manuscript; D. A. Moneret-Vautrin contributed to the analysis of the data from 333 cases recorded by the Allergy Vigilance Network and also to the writing the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM) adverse skin reactions, a 20-year survey. *Allergy* 1997;**52**:388–393.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**: 1200–1205.
3. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18820 patients. *BMJ* 2004;**329**:15–19.
4. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report – Second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. *J. Allergy Clin Immunol* 2006;**117**: 391–397.
5. Moneret-Vautrin DA, Morisset M, Flabbée J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005;**60**:443–451.

6. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;**30**:1144–1150.
7. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J All Clin Immunol* 2009;**123**:434–442.
8. Van Der Klauw MM, Stricker BHC, Herings RMC, Cost WS, Valkenburg HA, Wilson JHP. A population based case-cohort study of drug-induced anaphylaxis. *Br J Clin Pharmacol* 1993;**35**:400–408.
9. Thiessard F, Roux E, Miremont-Salame G, Fourrier-Reglat A, Haramburu F, Tuber-Bitter P et al. Trends in spontaneous adverse drug reaction reports to the French Pharmacovigilance system (1986–2001). *Drug Saf* 2005;**28**:731–740.
10. Simons FE, Ardusso L, Bilo MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol* 2011;**127**:587–593.
11. Worm M, Timmermans F, Moneret-Vautrin DA, Muraro A, Malmheden-Yman I, Lövik M et al. Towards a European registry of severe allergic reactions: current status of national registries and future needs. *Allergy* 2010;**65**:671–680.
12. Ring J, Behrendt H. Anaphylaxis and anaphylactoid reactions. Classification and pathophysiology. *Clin Rev Allergy Immunol* 1999;**17**:387–399.
13. Brockow K, Romano A, Blanca M, Ring J, Picheler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;**57**:45–51.
14. Moneret-Vautrin DA. Skin tests for diagnosis of curare allergy. *Ann Fr Anesth Reanim* 2002;**21**(Suppl 1):97–107.
15. 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**:961–972.
16. Demoly P. Anaphylactic reactions – value of skin and provocation tests. *Toxicology* 2005;**209**:221–223.
17. 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.
18. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly J. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;**140**:1001–1006.
19. Brockow K, Christiansen C, Kanny G, Clément O, Barbaud A, Bircher AJ et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;**60**:150–158.
20. Falcao H, Lunet N, Gomes E, Cunha L, Barros H. Drug allergy in university students from Porto, Portugal. *Allergy* 2003;**58**:1210.
21. Gomes E, Cardoso M, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004;**34**:1597–1601.
22. Ponvert C, Perrin Y, Bados-Allierat A, Le Bourgeois M, Karila C, Delacourt C et al. Allergy to beta lactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol* 2011;**22**:411–418.
23. Moneret-Vautrin DA, Mertes PM. Anaphylaxis to general anesthetics. *Chem Immunol Allergy* 2010;**95**:180–189.
24. Beaudouin E, Kanny G, Blanloeil Y, Guilloux L, Renaudin JM, Moneret-Vautrin DA. Anaphylactic shock induced by gadoterate meglumine. *Allerg Immunol* 2003;**35**:382–385.
25. Hasdenteufel F, Luyasu S, Renaudin JM, Paquay JL, Carbutti G, Beaudouin E et al. Anaphylactic shock after first exposure to gadoterate meglumine: two cases reported. *J Allergy Clin Immunol* 2008;**121**: 527–528.
26. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadona P et al. for the ENDA and the EAACI Interest group on Drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media-a European multicenter study. *Allergy* 2009;**64**:234–241.
27. 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.
28. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J et al. Hypersensitivity to non steroidal anti-inflammatory drugs (NSAIDs)- classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy* 2011;**66**:818–829.
29. Caimmi S, Caimmi D, Bousquet PJ, Demoly P. How can we better classify NSAID hypersensitivity reactions? – Validation from a large database *Int Arch Allergy Immunol* 2012;**159**:306–312.
30. Van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Different risks for NSAID-induced anaphylaxis. *Ann Pharmacother* 2002;**36**:24–29.
31. Riemer AB, Gruber S, Pali-Schöll I, Kinaciyan T, Untersmayr E, Jensen-Jarolim E. Suppression of gastric acid increases the risk of developing immunoglobulin E-mediated drug hypersensitivity: human diclofenac sensitization and a murine sensitization model. *Clin Exp Allergy* 2010;**40**:486–493.
32. Harrer A, Lang R, Grims R, Braitsch M, Hawranek T, Aberer W et al. Diclofenac hypersensitivity: antibody responses to the parent drug and relevant metabolites. *PLoS One* 2010;**5**:e13707.
33. Kvedariene V, Benchericua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blind trial. *Clin Exp Allergy* 2002;**32**:1366–1369.
34. Rutkowski K, Nasser SM, Ewan PW. Paracetamol hypersensitivity: clinical features, mechanism and role of specific IgE. *Int Arch Allergy Immunol* 2012;**159**:60–64.