

Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974–1994) and review of the literature

M. M. VAN DER KLAUW*†, J. H. P. WILSON† and B. H. CH. STRICKER*‡

*Drug Safety Unit of the Dutch Inspectorate for Health Care, Rijswijk †Department of Internal Medicine II, Erasmus University Medical School, Rotterdam and ‡Pharmacoepidemiology Unit, Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands

Summary

Background Since 1963, the Drug Safety Unit of the Dutch Inspectorate for Health Care (DSU) holds a voluntary reporting system.

Objective To analyse all reports received in the years 1974 to 1994, registered as anaphylaxis or as a diagnosis that could contain cases of anaphylaxis.

Methods All reports were classified as probable or possible anaphylaxis according to previously described criteria and the causal relationship between exposure and anaphylaxis was assessed.

Results Nine hundred and ninety-two reports possibly concerning anaphylaxis were received between 1974 and 1994. Fifty-six were unclassifiable. The remaining 936 reports concerned 326 men and 610 women. Three hundred and forty-five reports were classified as anaphylaxis probable, 485 as anaphylaxis possible, and 106 as anaphylaxis unlikely by previously specified criteria. Drugs frequently associated with anaphylaxis (causal relationship certain or probable) were: glafenine (326 reports classified as anaphylaxis probable or possible), combination preparations with (propy)phenazone or propyphenazone/phenacetine (39), diclofenac (30), dextran (20), ibuprofen (14), floctafenine (12), allergen extracts (12), sulfamethoxazole with trimethoprim (12), and trimethoprim (11). There is probably substantial under-reporting as well as reporting bias in these data. Furthermore, many reports were classified as possible and not as probable anaphylaxis because the temporal relationship was unknown or not reported.

Conclusion Drugs that caused anaphylaxis most frequently were glafenine, NSAID and certain antibiotics. Data from a voluntary reporting system such as the DSU are valuable as an early warning system for drugs that may induce anaphylactic reactions.

Keywords: drug-induced, anaphylaxis, adverse reaction, reporting system, glafenine, propyphenazone, diclofenac, dextran, ibuprofen

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Introduction

Anaphylaxis is usually defined as an acute allergic reaction that results from the release of pharmacologically active mediators from tissue mast cells and peripheral

blood basophils. IgE antibodies bind to mast cells, cause activation and subsequent degranulation. An anaphylactoid reaction is a similar reaction, but not mediated by IgE antibodies, and not requiring previous exposure. Since both syndromes are clinically indistinguishable, in this study we used the term anaphylaxis to describe both [1,2].

Drug-induced anaphylaxis is a very serious adverse event, and may be fatal. Data regarding the incidence of

Correspondence: Dr B. H. Ch. Stricker, Pharmacoepidemiology Unit, Department of Epidemiology and Biostatistics, Room Ee 2126, Erasmus University Medical School, Dr Molewaterplein 50, 3015 GD Rotterdam, The Netherlands.

drug-induced anaphylaxis are limited. Antibiotics and radiocontrast agents seem to be the most common causes of serious anaphylaxis, with rates of about 1 in 5000 exposures [2]. Drugs which cause anaphylaxis are mainly known from case reports and some small case series. Therefore, we present an analysis of all 992 reports of drug-induced anaphylaxis received by the Drug Safety Unit of the Dutch Inspectorate for Health Care (DSU) from 1974 to 1994 and a review of the literature.

Material and methods

Setting

Since 1963, the DSU holds a voluntary reporting system, which has comparable procedures to the yellow card system in the United Kingdom. The number of reported reactions per year has grown to 1780 in 1994. Reports are made by physicians (mostly general practitioners). A small number of reports are made by a pharmacist. In this case, the prescribing physician is contacted for more detailed information regarding the adverse event.

In this study, the reports received from 1974 to 1994 were analysed. All reports registered as anaphylaxis, anaphylactic shock or reaction, anaphylactoid shock or reaction, allergic reaction, face oedema, and periorbital or eyelid oedema were included. Also included were combinations of skin reactions (such as rash, urticaria, angioedema or pruritus) with respiratory tract reactions (such as bronchospasm, dyspnoea, laryngeal oedema or stridor) or with cardiovascular reactions (such as hypotension, syncope, circulatory failure or collapse) or with death, and combinations of respiratory reactions with death. All reports were classified according to probability of anaphylaxis by the criteria shown in Fig. 1 and described earlier [3]. The reports had to contain details on gender and date of birth of the patient, and had to be confirmed by a medical practitioner in order to be classifiable.

Symptoms characteristic of anaphylaxis were symptoms out of two or more of the following four systems, except for a combination of only the cardiovascular and the gastro-intestinal system:

- 1 cardiovascular system;
- 2 respiratory system;
- 3 skin and conjunctiva; and
- 4 gastro-intestinal system (e.g. nausea, vomiting, diarrhoea, abdominal pain).

Symptoms compatible with, but not characteristic of, anaphylaxis were symptoms out of only one of the above mentioned systems (with the exception of the gastro-intestinal system) or a combination of cardiovascular

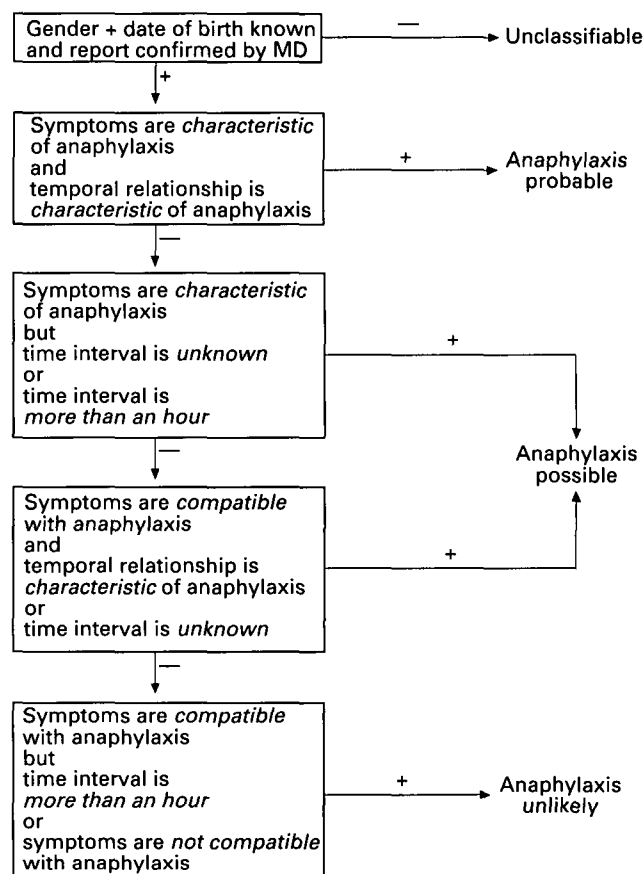


Fig. 1. Model of classification of anaphylaxis.

and gastro-intestinal symptoms. Otherwise, symptoms were not compatible with anaphylaxis [3].

The temporal relationship was considered as characteristic of anaphylaxis if the reaction occurred within 1 h after exposure to the causative agent, or was described as 'shortly' or 'immediately' after exposure.

Assessment of causal relationship

The causal relationship between exposure to the drug and anaphylaxis was classified as 'causal relationship probable' if the patient had been exposed to one suspected cause within 1 h before developing anaphylaxis, and as 'causal relationship certain' if, in addition, there had been a positive reaction to rechallenge. The classification 'causal relationship possible' was used if the patient had been exposed to more than one potential cause within 1 h before anaphylaxis. The classification 'causal relationship unlikely' was used if the temporal relationship was incompatible, i.e. in cases in which the exposure did not precede the reaction (challenge), in which discontinuation was not followed by recovery of a reversible event (dechallenge), or in which continuation

Table 1. Symptoms mentioned in the reports classified as probable and possible anaphylaxis (% of total in brackets)

Symptom	Anaphylaxis probable (<i>n</i> = 345)	Anaphylaxis possible (<i>n</i> = 485)	Total (<i>n</i> = 830)
Collapse or immeasurable blood pressure	142 (41.2%)	178 (36.7%)	320 (38.6%)
Blood pressure < 100 mm Hg and no collapse, or hypotension during surgery	54 (15.7%)	27 (5.6%)	81 (9.6%)
Blood pressure > 100 mm Hg, but lower than normal (hypertensive patient)	6 (1.7%)	6 (1.2%)	12 (1.4%)
Blood pressure lowered, exact value unknown	49 (14.2%)	35 (7.2%)	84 (10.1%)
Blood pressure not lowered	27 (7.8%)	28 (5.8%)	55 (6.6%)
Blood pressure unknown	67 (19.4%)	211 (43.5%)	278 (33.5%)
Urticaria	96 (27.8%)	117 (24.1%)	213 (25.7%)
Erythema or generalized flushing	181 (52.5%)	165 (34.0%)	346 (41.7%)
Angioedema	145 (42.0%)	206 (42.5%)	351 (42.3%)
Pruritus	124 (35.9%)	113 (23.3%)	237 (28.6%)
Other type of skin reaction	10 (2.9%)	18 (3.7%)	28 (3.4%)
Skin reaction of unknown type	1 (0.3%)	4 (0.8%)	5 (0.6%)
No skin reaction	12 (3.5%)	16 (3.3%)	28 (3.4%)
Skin reaction unknown	23 (6.7%)	120 (24.7%)	143 (17.2%)
Oedema of the glottis	23 (6.7%)	23 (4.7%)	46 (5.5%)
Bronchospasm	66 (19.1%)	39 (8.0%)	105 (12.7%)
Laryngeal spasm or laryngeal oedema	13 (3.8%)	3 (0.6%)	16 (1.9%)
Dyspnoea, but type unknown	101 (29.3%)	79 (16.3%)	180 (21.7%)
No dyspnoea	42 (12.2%)	28 (5.8%)	70 (8.4%)
Dyspnoea unknown	106 (30.7%)	316 (65.2%)	422 (50.8%)
Nausea/vomiting	70 (20.3%)	49 (10.1%)	119 (14.3%)
Diarrhoea/faecal urge	45 (13.0%)	24 (4.9%)	69 (8.3%)
Abdominal spasm/stomach pain	33 (9.6%)	20 (4.1%)	53 (6.4%)
No gastro-intestinal symptoms	11 (3.2%)	7 (1.4%)	18 (2.2%)
Gastro-intestinal symptoms unknown	205 (59.4%)	366 (75.5%)	571 (68.8%)

or readministration (rechallenge) did not cause a relapse.

Results

Nine hundred and ninety-two reports were analysed, of which 56 were unclassifiable because of lack of data. The remaining 936 reports concerned 345 cases in which anaphylaxis was probable, 485 cases in which anaphylaxis was possible, and 106 cases in which anaphylaxis was unlikely.

Symptoms mentioned in the reports classified as probable and possible anaphylaxis are summarized in Table 1.

Descriptions of reports concerning age and gender, the temporal relationship between exposure and outcome, where and how patients were treated and patient recovery are summarized in Table 2. In those reports classified as probable anaphylaxis, the temporal relationship

between exposure and outcome was less than 1 h in all reports. Mostly, reports were classified as possible and not as probable anaphylaxis because the exact temporal relationship between exposure and outcome was not reported or unknown, which was the case in 332 out of 485 reports (68.5%).

Of the 830 reports of probable or possible anaphylaxis, 206 patients (24.8%) were admitted to a hospital or treated in the accident and emergency department, 441 (53.1%) were treated by the general practitioner, or not treated at all, and in 117 patients (14.1%) anaphylaxis occurred inside a hospital.

Treatment consisted mostly of adrenaline, corticosteroids or antihistamines, or a combination of two of these or all three. In 400 reports, treatment was unknown or not mentioned.

Of 345 patients with probable anaphylaxis, two recovered with irreversible damage (one vascular occlusion and one myocardial infarction), and 14 people died due

Table 2. Descriptives

	Anaphylaxis probable (<i>n</i> = 345)	Anaphylaxis possible (<i>n</i> = 485)
	<i>n</i> (%)	<i>n</i> (%)
<i>Gender</i>		
Male/female	124/221	176/309
<i>Age (yr)‡</i>		
Males	47 (35–61)	45 (33–60)
Females	44 (31–60)	48 (34–60)
<i>Temporal relationship</i>		
< 15 min	149 (43.2)	40 (8.2)
15–30 min	88 (25.5)	21 (4.3)
30–60 min	41 (11.9)	17 (3.5)
'Within 1 h' or 'directly after administration'	67 (19.4)	22 (4.5)
1–2 h		29 (6.0)
> 2 h		24 (4.9)
Not reported or unknown		332 (68.5)
<i>Admission</i>		
Admitted to hospital	102 (29.6)	90 (18.6)
Treated in A & E*	7 (2.0)	7 (1.4)
Treated by GP† or not treated	158 (45.8)	283 (58.4)
During admission	54 (15.7)	63 (13.0)
Not reported or unknown	24 (7.0)	42 (8.7)
<i>Treatment</i>		
Adrenaline	5 (1.4)	4 (0.8)
Corticosteroid drug	22 (6.4)	20 (4.1)
Antihistaminic drug	31 (9.0)	31 (6.4)
Adrenaline and corticosteroid drug	15 (4.3)	11 (2.3)
Adrenaline and antihistaminic drug	12 (3.5)	12 (2.5)
Corticosteroid and antihistaminic drug	45 (13.0)	39 (8.0)
Adrenaline, corticosteroid and antihistaminic drug	19 (5.5)	11 (2.3)
Other combination	56 (16.2)	31 (6.4)
No treatment	26 (7.5)	40 (8.2)
Treatment unknown or not mentioned in report	114 (33.0)	286 (59.0)
<i>Recovery</i>		
Complete	319 (92.5)	444 (91.5)
Incomplete or with irreversible damage	2 (0.6)	4 (0.8)
Died	14 (4.1)	7 (1.4)
Unknown	10 (2.9)	30 (6.2)

*A & E = accidents and emergency department, admission < 0.5 day

†GP = General practitioner

‡Median age (25–75%)

to the anaphylaxis. Of 485 patients with possible anaphylaxis, two still had exanthema at the time of reporting, two recovered with irreversible damage (one myocardial infarction and one suffered a cardiac arrest and had post-resuscitation rib fractures and amnesia), and seven died. The drugs responsible for fatal anaphylaxis were: radiocontrast agents (8), dextran (3), glafenine (2), immunotherapy for allergy (2), protamine (1), penicillin (1), tetracosactide (1), metoprolol (1),

erythromycin (1) and butylscopolamine with metimazole (1).

One hundred and ninety-nine out of 345 patients with probable anaphylaxis had used the causative drug before, and of them 89 had had a similar reaction to the drug previously, or had a positive rechallenge to the drug. The reactions occurring previously mostly consisted of a less serious reaction (e.g. erythema or urticaria) than anaphylaxis, but sometimes they consisted of

Table 3. Classification of anaphylaxis and causal relationship

	Anaphylaxis probable	Anaphylaxis possible	Total
Causal relationship certain	77	80	157
Causal relationship probable	254	362	616
Causal relationship possible	13	42	55
Causal relationship unlikely	1	1	2
Total	345	485	830

a full-blown anaphylactic reaction. Additionally, two patients experienced anaphylaxis during immunotherapy for allergy. Of the 485 patients with possible anaphylaxis, 230 had used the drug before, and of these 94 had had a previous reaction, or had a positive rechallenge. Also, two additional patients experienced anaphylaxis during immunotherapy for allergy. Of the reports of probable anaphylaxis, 26 patients had never used the drug before, and in 120 reports this was unknown. For the reports of possible anaphylaxis these figures were 27 (never used before) and 228 (unknown). In the reports classified as probable anaphylaxis, the causal relationship between exposure and anaphylaxis was certain in 77 reports, probable in 254 reports, possible in 13, and unlikely in 1 (Table 3). In the reports classified as possible anaphylaxis, the causal relationship between exposure and anaphylaxis was certain in 80 reports, probable in 362 reports, possible in 42, and unlikely in 1.

The most frequent causes of drug-associated anaphylaxis are specified in table 4 for the reports classified as probable and possible anaphylaxis. The causative drugs are shown for those reports in which the causal relationship was classified as certain ($n = 157$) or as probable ($n = 616$). Glafenine was the drug most frequently associated with anaphylaxis, followed by combination preparations of propyphenazone, phenazone and phenacetine, non-steroidal anti-inflammatory drugs (NSAID) (diclofenac, ibuprofen, and naproxen), dextran, floctafenine, allergen extracts, and antibiotics (trimethoprim with or without sulfamethoxazole, amoxicillin, furoxone and nitrofurantoin).

Discussion

This study describes 992 cases of drug-associated anaphylaxis which were reported during a period of 20 years. This amounts to a mean of ± 50 reports of drug-associated anaphylaxis per year in a country with 13 000 000 to 15 000 000 people in those years. Probably, the frequency of drug-induced anaphylaxis is much higher, as even though anaphylaxis is a serious adverse

reaction, under-reporting is substantial. In two studies performed by the authors, only 8% [3] and 4% [4] of cases of drug-induced anaphylaxis had been reported to the DSU. The clinical pattern of anaphylaxis in our study is in line with the medical literature on this topic. Because serious reactions are more readily reported, however, the prevalence of serious symptoms in our study (e.g. shock) may be over-represented. Of 773 reports of drug-induced anaphylaxis with a causal relationship certain or probable, 326 were associated with glafenine, the next most frequently reported drugs being combination preparations of paracetamol and (propy)phenazone and phenacetine (45 reports), diclofenac (30 reports) and dextran (20 reports). The large number of reports on glafenine is especially important in view of the small sales figures the drug had in The Netherlands when compared to the other analgesics and NSAID. Part of this is probably due to reporting bias; part, however, reflects the relatively high incidence of glafenine-induced anaphylaxis, as was found in a nationwide study performed in The Netherlands [3]. Glafenine is an analgesic drug, which was withdrawn worldwide in 1992 [5].

Other drugs often reported as a cause of anaphylaxis were ibuprofen, floctafenine, allergen extracts, the combination of sulfamethoxazole with trimethoprim or trimethoprim alone, amoxicillin, blood volume expanders, naproxen, mebhydroline, polidocanol, cimetidine, ranitidine, and tolmetine. Other antibiotics than the aforementioned were less often reported, partly due to the fact that most reports were made by general practitioners, and probably partly due to under-reporting.

Of 345 reports classified as probable anaphylaxis, symptoms developed later than 30 min after exposure in 41 reports (11.9%). These data support the policy of observing a patient for at least 1 h after administration of antigen during treatment with immunotherapy for allergy.

Out of 830, 21 patients died, and 6 suffered irreversible damage due to the anaphylaxis, stressing the severity of this adverse event.

Unfortunately, because the temporal relationship was not explicitly stated, a relatively large number of reports did not contain enough information for classification as probable anaphylaxis.

Most publications on drug-induced anaphylaxis consist of case-reports. Anaphylaxis associated with almost all of the 17 most frequently reported drugs in Table 4 was described in the literature. Examples are anaphylaxis associated with glafenine [6–11], paracetamol [12–14], diclofenac [15–17], dextran and other blood volume expanders [18–20], ibuprofen [21], naproxen [22], cimetidine [23,24], ranitidine [25] and tolmetine [26–30]. The DSU published case reports or case series on anaphylaxis associated with glafenine [3,4,31], paracetamol [32],

Table 4. Causes of drug-induced anaphylaxis with a causal relationship certain or probable; separate columns for anaphylaxis probable, anaphylaxis possible and the total number (anaphylaxis probable and anaphylaxis possible). (Number of deaths between brackets)

Drug	Anaphylaxis probable (n = 331)	Anaphylaxis possible (n = 442)	Total (n = 773)
Glafenine	146 (2)	180	326 (2)
Propyphenazone/paracetamol, propyphenazone/phenacetine or propyphenazone/carzenide	17	20	37
Diclofenac	12	18	30
Dextran	9 (2)	11 (1)	20 (3)
Ibuprofen	5	9	14
Floctafenine	9	3	12
Allergen extracts	7 (2)	5	12 (2)
Sulfamethoxazole with trimethoprim	4	8	12
Trimethoprim	4	7	11
Amoxicillin	6	3	9
Blood expanders (gelatine)	3	5	8
Naproxen	2	6	8
Mebhydroline	2	4	6
Polidocanol	5	1	6
Cimetidine	2	4	6
Paracetamol +/- coffein	1	5	6
Ranitidine	2	3	5
Tolmetine	3	2	5
Fytomenadione	2	2	4
Chlorhexidine	5	2	7
Furoxone	-	4	4
Nitrofurantoin	-	4	4
Ketoconazole	2	2	4
Atracurium	2	2	4
Amidotrizoic acid*	3 (2)	1	4 (2)
Omeprazole	-	3	3
Metimazole/butylscopolamine	-	3	3
Domperidone	3	-	3
Tetracosactide	2	1 (1)	3 (1)
Indometacine	1	2	3
Acetylsalicylic acid	1	2	3
Combinations with ergotamine**	1	2	3
Expectorants, combination preparations	1	2	3
Acetylcystein	-	3	3
Terfenadine	2	1	3
Metrizoic acid*	2 (2)	1	3 (2)
Patent blue	1	2	3
Metimazole/pitophenone/phenpiveriniumbromide	-	2 (1)	2 (1)
Vitamin B complex	1	1	2
Heparin	2	-	2
Phenazone/phenazonesalicylate/coffein/kinine	-	2	2
Ticlopidine	-	2	2
Parenteral ferri preparation	-	2	2
Urapidil	-	2	2
Captopril	-	2	2
Enalapril	-	2	2
Hydrochorthiazide with potassium sparing drugs	2	-	2
Terbinafine	-	2	2

Table 4. Continued

Drug	Anaphylaxis probable (n = 331)	Anaphylaxis possible (n = 442)	Total (n = 773)
Methoxsalene	-	2	2
Ergometrine	-	2	2
Medroxyprogesterone	2	-	2
Nalidixinic acid	1	1	2
Pipemidinic acid	2	-	2
Amoxicillin with clavulanic acid	1	1	2
Piroxicam	-	2	2
Ketoprofen	1	1	2
Prilocain	1	1	2
Bromocriptine	-	2	2
Maprotiline	-	2	2
Mefloquine	1	1	2
Bromhexine	2	-	2
Promethazine	2	-	2
Protamine	1 (1)	1	2 (1)
Joxitalamic acid*	2 (1)	-	2 (1)
Diagnostic radiopharmaca	2	-	2
Miscellaneous (all mentioned once)	41 (2)	76 (2)	117 (4)
Total	331	442	773

* = radiocontrast agents.

** = ergotamine/cyclizine/coffein or ergotamine/cyclizine or ergotamine/cafein.

floctafenine [33], polidocanol [34], cinoxacin [35], iso-flurane [36], chlorhexidine [37], bromhexine [38] and ketoconazole [39].

Three studies were performed on drug-induced anaphylaxis with the use of reporting systems, two focusing on plasma expanders [40,41], and one on NSAID's [42]. In the Swedish study [40] all reports on dextran-induced anaphylaxis during the period 1970–1979 were studied. Since 1974 reporting of fatal and serious adverse reactions has been mandatory in Sweden. The authors estimated the incidence of severe anaphylaxis per unit administered to be 0.013% for dextran 40 and 0.025% for dextran 70. In the German study [41], during the period 1969 to 1976 all reports on transfusion emergencies following the administration of colloid plasma expanders dextran, gelatin and starch were studied. Since in Germany reporting of adverse reactions to drugs was not mandatory, an incidence could not be estimated. The study on NSAID [42] was performed with data from the voluntary Adverse Drug Reaction Reporting System (ADRRS), a system administered by the American Academy of Dermatology. There were four reports of drug-induced anaphylaxis during the period December 1980 to July 1983, all associated with zomepirac.

Only a small number of epidemiological studies on drug-associated anaphylaxis have been performed [43–46], probably because anaphylaxis is a rare adverse

drug reaction. All patients admitted with a clinical diagnosis of anaphylaxis, anaphylactic reaction or anaphylactic shock at the Mayo Clinic and affiliated hospitals were studied during a 3.5 year period [43]. Only 23 out of 179 cases of anaphylaxis were attributed to drugs in this study. In a study performed by Rudolph *et al.* [44], reactions to penicillin treatment in patients visiting venereal disease clinics were studied. The incidence of anaphylaxis among these patients was 0.04% in 1969, with the incidence of moderate to severe anaphylaxis being 0.018% among treated patients. From the data in this survey and previous surveys conducted in 1954, 1959 and 1964 combined, the incidence of moderate to severe anaphylaxis was estimated at 0.025% of treated patients. The authors estimated the fatality rate to be 0.001% of treated patients. In a study performed by Porter and Jick [45] adverse reactions to drugs during hospitalization at selected medical wards in the USA and several other countries were studied. Drug-induced anaphylaxis was reported in 0.04% of all patients (12 out of 32812 patients, 9 following intravenous therapy). In a Danish study [46], during a 13-year period only 20 cases of anaphylaxis were found in the catchment area of one specific hospital, of which 10 were caused by drugs (seven by penicillin and three by aspirin). None of these cases were reported to the national health authorities.

Some multi-centre trials have been performed, examining the incidence of anaphylaxis due to plasma expanders [47–50] and penicillins [51], the more frequent causes of anaphylaxis. Ring and Messmer [47] estimated the incidence of anaphylaxis at 0.033% of units of colloid solutions used in general, of which 0.069% were for dextran 60/75, 0.007% for dextran 40, and 0.115% for gelatin. In a multicentre prospective study on polygeline [48] only one patient (0.09%) developed systemic anaphylaxis. In a prospective study on dextran 70-induced anaphylaxis [49], 14 females experienced anaphylaxis (0.24%). In a prospective study on plasma substitutes [50], 43 out of 19 593 patients developed an anaphylactoid reaction (0.219%). The incidence of anaphylaxis due to gelatins was 0.345%, due to dextrans 0.273%, due to albumins 0.099%, and due to amidons 0.058%. Unfortunately, the exclusion criteria applied to the cases were not applied to the control group.

One of the most frequently studied drugs causing anaphylaxis is penicillin. In a review article, Weiss and Adkinson [52] reported the frequency of allergic reactions to penicillin to vary from 0.7% to 8% of treatment courses in various studies. According to Idsoe *et al.* [53] the frequency of anaphylaxis due to penicillin varies from 0.01% to 0.035%. In a study performed by the International Rheumatic Fever Study Group [51], 1790 patients from 11 countries were enrolled in a prospective study to determine the incidence of allergic reactions to monthly intramuscular benzathine penicillin. Four patients experienced anaphylaxis, which means a case incidence of 0.2% and an injection frequency of 0.012%. One of these four patients died (case fatality rate 0.05%).

Radiocontrast materials are also well-known causes of anaphylaxis. Siegle *et al.* examined a group of patients who previously reacted with anaphylaxis to intravenously administered ionic high-osmolar contrast material. During the study 291 patients received iohexol, of whom 16 (5.5%) experienced anaphylaxis. It appeared that the more serious the prior reaction, the higher the rate was of repeat reactions [54].

In a study by Matloff *et al.* [55] all systemic reactions during 1 year due to immunotherapy were included. Out of 27 806 injection visits, 143 resulted in systemic reactions (0.51%), of which 17% needed adrenaline therapy.

Our study shows the overview of reports of drug-induced anaphylaxis in the Netherlands in the past 20 years. For some of the drugs this adverse reaction was unknown at the time of reporting. Most of these associations have been published by the DSU. In some (e.g. glafenine), data from the DSU have been used as a signal for a high frequency of adverse reactions. Because of the low frequency of drug-induced anaphylaxis, this adverse reaction is hard to investigate, which the above overview

of the literature shows. Prospective studies are very difficult to perform. Also, these are limited to certain classes of drugs, e.g. drugs which are used relatively frequently in an easily accessible population, e.g. blood volume expanders which are exclusively used in a hospital setting. Therefore, a reporting system for adverse reactions remains essential for signal generation of unknown and unexpected adverse reactions to drugs. For a reporting system to function properly, several items are of importance. First, doctors should report all serious and unexpected adverse reactions. Second, the possibility of obtaining further details from reporters is essential. Third, all unknown or unexpected adverse reactions should be reported in the medical literature.

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