

A population based case-cohort study of drug-induced anaphylaxis

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- 1 In order to determine the risk of anaphylaxis as an adverse reaction to drugs, a case-cohort study was performed. Cases consisted of all admissions in 1987 and 1988 to all Dutch hospitals with anaphylaxis as the principal diagnosis, and a random sample of admissions with related symptoms. Hospital discharge summaries were classified according to probability of anaphylaxis by a blinded Audit Committee. Of admissions classified as probable or possible anaphylaxis, the causative agent was assessed. The reference cohort consisted of all persons in the catchment area of a sample of pharmacies in The Netherlands, in the period between January 1, 1987 and December 31, 1988.
- 2 Out of 934 admissions, discharge summaries on 811 admissions were received, of which 727 contained enough clinical details. Out of 727, 391 were classified as probable or possible anaphylaxis. In 336 of these 391, anaphylaxis was reason for admission. This group consisted of 158 men and 178 women. Drug-induced anaphylaxis occurred in 107 patients.
- 3 Drug-induced anaphylaxis was most frequently caused by penicillins, analgesics and non-steroidal antiinflammatory drugs (NSAID) with the highest point estimate of the risk relative to all other drugs of 10.7, 6.9 and 3.7 respectively.
- 4 In the cases of probable anaphylaxis, the risk of anaphylaxis to glafenine relative to all other drugs was 167.7 in 1987 (95%-CI: 63.0-446.4) and 128.6 in 1988 (95%-CI: 50.4-328.5), to amoxycillin 15.2 in 1987 (95%-CI: 5.0-46.0) and 4.4 in 1988 (95%-CI: 1.03-18.9) and to diclofenac 6.1 in 1988 (95%-CI: 1.4-26.1).
- 5 The case-cohort design may be useful for postmarketing surveillance.

Keywords anaphylaxis glafenine amoxycillin diclofenac case-cohort study
adverse drug reaction postmarketing surveillance pharmacoepidemiology

Introduction

In many countries information on adverse reactions to drugs is collected by voluntary reporting of adverse reactions, predominantly by medical practitioners and pharmacists. Although voluntary reporting schemes are a useful resource for signal generation, the major limitation is that no insight is obtained into the incidence or relative risk of adverse reactions, due to non-recognition or underreporting of adverse reactions, false attribution of adverse events to drugs, reporting bias and the absence of reliable drug con-

sumption data. In the past 25 years associations between adverse events and drugs have been reported frequently in the medical literature and/or to reporting systems. The interpretation of such associations and their incidence has posed considerable problems to regulatory authorities. One example concerns the analgesic glafenine, an anthranilic acid derivative which was registered more than 20 years ago in several European, Asian, South-American and African countries. Since 1972 several cases of anaphylaxis have

been reported in the literature (Barral & Faivre, 1975; Cheymol *et al.*, 1985; Davido *et al.*, 1989; Faveret *et al.*, 1975; Fischbein *et al.*, 1984; Gaultier *et al.*, 1972; Grand & Despret, 1973; Journe *et al.*, 1980; Laine *et al.*, 1985; Maesen *et al.*, 1976; Meyboom, 1976; Michaud & Doublet, 1976; Sauder *et al.*, 1982; Sentilhes, 1978; Stricker *et al.*, 1991; Weber *et al.*, 1982) and several hundreds of cases have been reported to The Netherlands Centre for Monitoring of Adverse Reactions to Drugs. Since a high frequency of reporting does not prove that a particular adverse reaction has a high incidence, other methods than voluntary reporting had to be used to investigate further the hypothesis that anaphylaxis occurs more frequently in response to glafenine than to other analgesics. In a previous study with data of the year 1981 (Stricker *et al.*, 1991), it was demonstrated that the risk of anaphylaxis to glafenine was higher than to any other 'prescription only' drug available in The Netherlands. In order to assess whether the situation had changed in recent years after the adjustment of the data sheet in 1986 and in order to compare the risk of anaphylaxis to glafenine with the risk of anaphylaxis to similar drugs, this study was performed.

Methods

Design

In this study a case-cohort design was used (Prentice, 1986). The study base consisted of all persons in The Netherlands in 1987 or 1988 (the base cohort). All dispensing data over the years 1987 and 1988 from the representative sample of pharmacies were considered as a random exposure sample from the base cohort (the reference cohort). This sample was used as the reference source of exposure information. All instances of anaphylaxis in the study base as a reason for admission were defined as cases, of which the drug exposure was compared with that of the reference cohort.

Morbidity data

Anaphylaxis is an acute reaction which occurs within 1 h after exposure to a substance and which can involve the cardiovascular system (e.g. hypotension), the respiratory system (e.g. bronchospasm), the skin (e.g. urticaria) and the gastrointestinal system (e.g. diarrhoea) (Wasserman & Marquardt, 1988). Although immunologically there is a difference between anaphylactic and anaphylactoid reactions, it is clinically not possible to differentiate between both types of reaction, and in the medical literature both mechanisms are referred to as anaphylaxis (Bochner & Lichtenstein, 1991). Therefore, in this study both types of reaction were included.

Data on morbidity were obtained from a nationwide computerized register of hospital diagnoses, in which admission data are filed on a continuing basis from all general and university hospitals in The Netherlands. Data include gender, date of birth, admission and discharge, one principal diagnosis (mandatory) and

up to nine additional diagnoses (optional) for every admission. Diagnoses are all coded according to the ICD-9-CM. We included all admissions in the study concerning patients who had been discharged in 1987 or 1988 with one of the following principal diagnoses: 995.0 (anaphylactic shock, including allergic shock, anaphylactic reaction and anaphylaxis: 253 admissions), 995.4 (shock due to anaesthesia: 0 admissions), 999.4 (anaphylactic shock due to serum: 3 admissions) and 989.5 (venom; insect stings/bites: 202 admissions). Code 989.5 was included because cases of anaphylaxis to insects could have been classified as an insect sting or bite. Because some cases of anaphylaxis could have been classified under another diagnosis code (e.g. urticaria or allergy), a random sample was obtained of the following principal diagnoses: 693.0 (dermatitis due to drugs and medicaments: 120 admissions), 695.0 (toxic erythema: 36 admissions), 708.0 (allergic urticaria: 60 admissions), 995.1 (angioneurotic oedema: 80 admissions), 995.2 (unspecified adverse effect of drug, medicament and biological: 120 admissions) and 995.3 (allergy, unspecified: 60 admissions).

Exposure data

Data on dispensed drugs were obtained from a representative sample of 28 pharmacies from different parts of The Netherlands with a catchment area comprising a population of approximately 100,000 persons (562,855 prescriptions) in 1987 and 150,000 persons (832,856 prescriptions) in 1988 (= 1% of the Dutch population), as kept by the PHARMO exposure database (Herings *et al.*, 1992). This population formed the reference cohort. The vital statistics concerning age (stratified in 15-year age groups) and gender in this reference cohort were the same as in the population in The Netherlands (Chi square = 8.1, 11 degrees of freedom; $P = 0.7$). Numbers of prescriptions, exposed individuals and days at risk were used as the denominator in the relative risk assessments. Days at risk were calculated by dividing the total number of dispensed tablets/capsules per patient by the prescribed daily intake of tablets/capsules.

Procedures

The physicians involved in the treatment of the patients with anaphylaxis were asked to provide clinical details at admission by sending an anonymised copy of the discharge summary of the patients in the study. If the copy of the discharge summary did not contain enough details, further information was requested.

An Audit Committee of three experienced consultants in internal medicine assessed the clinical details, blinded with regards to the identity of the patient, physician and hospital, and all possible causes of anaphylaxis. Description of symptoms and signs and of the course of the illness during admission were left unchanged. Every admission was analysed according to a predefined algorithm by which each admission was classified as either 'anaphylaxis probable', 'anaphylaxis possible', 'anaphylaxis unlikely' or 'admission unclassifiable'. Discharge summaries had to contain details on gender, date of birth and admission of the patient and symptoms of the reaction. If not available,

the admission was judged as 'admission unclassifiable'. An admission was classified as 'anaphylaxis probable' if the patient had suffered from symptoms characteristic of anaphylaxis, i.e. symptoms out of two or more of the following four systems (with the exception of a combination of system 1 and 4) and if the reaction had occurred within 1 h after exposure to the causative agent (or had been specified as 'shortly' or 'immediately' after exposure):

1. Cardiovascular system: collapse, loss of consciousness, hypotension (systolic blood pressure ≤ 100 mm Hg and symptoms characteristic of hypotension or, in case of hypertension, a blood pressure that gave symptoms characteristic of hypotension).
2. Respiratory system: rhinitis, swelling of the uvula or pharynx, laryngeal edema (stridor), bronchospasm (dyspnea, wheezing, asthma).
3. Skin and conjunctiva: pruritus, erythema, urticaria, angioedema, conjunctivitis.
4. Gastrointestinal system: nausea, vomiting, diarrhoea, fecal urge, abdominal pain or spasm.

If the patient had suffered from symptoms compatible with—but not characteristic of—anaphylaxis, i.e. symptoms out of only one of the systems 1, 2 or 3 or the combination of system 1 and 4, an admission was classified as 'anaphylaxis possible' if the reaction occurred within 1 h or if the time interval between exposure and reaction was unknown. If the symptoms were characteristic of anaphylaxis, but the reaction had occurred later than an hour after exposure or this time period was unknown the admission was also classified as 'anaphylaxis possible'. In any other case the classification was 'anaphylaxis unlikely'. Each member of the Audit Committee classified first every individual admission separately. Subsequently, final classification was decided on by consensus or by majority of votes. If no agreement was attained, the admission was classified as 'admission unclassifiable'. An anaphylactic reaction was classified as severe if it was generalized and potentially life-threatening. This was the case if the patient was suffering from cardiovascular or respiratory symptoms or if there was irreversible damage (e.g. myocardial infarction).

In all cases of 'anaphylaxis probable' or 'anaphylaxis possible' in which the reaction had been the reason for admission, the causal relationship between exposure and reaction was assessed according to previously defined and accepted criteria (Bégaud *et al.*, 1985). Basically, the exposure-anaphylaxis-association was classified as 'causal relationship probable' if the patient had been exposed to one suspected cause shortly before developing anaphylaxis, and as 'causal relationship certain' if, in addition, there had been a positive reaction to rechallenge. The exposure-anaphylaxis-association was classified as 'causal relationship possible' if the patient had been exposed to more than one potential cause shortly before anaphylaxis. The exposure-anaphylaxis-association was classified as 'causal relationship unlikely' if the temporal relationship was incompatible. Also, 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 or readministration (rechallenge) did not

cause a relapse, were classified as 'causal relationship unlikely'.

Data analysis

An estimation was made of the relative risk (RR) of responding to drug X with anaphylaxis compared with drug Y, classified according to the Anatomical Therapeutic Chemical (ATC) system. Every separate admission classified as 'anaphylaxis probable' was considered as a case of anaphylaxis. The relative risk was assessed as follows:

$$RR = \frac{\frac{\text{number of cases of anaphylaxis due to drug X}}{\text{number of cases of anaphylaxis due to drug Y}}}{\frac{\text{number of prescriptions for drug X in reference cohort}}{\text{number of prescriptions for drug Y in reference cohort}}}$$

Point estimates were calculated with their 95% confidence intervals (Miettinen, 1982). Similarly, relative risk estimations were performed with, in the denominator, the number of exposed individuals and the total number of days at risk per drug. Also, relative risk estimations were performed with, in the denominators of the upper and lower quotient, the number of all cases of anaphylaxis to all drugs except drug X, respectively the total number of prescriptions for all drugs except drug X. In order to see whether this would influence the relative risk estimation, re-analyses were performed with admissions classified as 'anaphylaxis possible'.

The inter-observer agreement in the Audit Committee was analysed by a weighted kappa test (Fleiss, 1981).

Results

Physicians responded to requests for information in 811 out of 934 admissions (87%). In 84 admissions the data were insufficient, either due to lack of clinical details ($n = 9$), or because the consultant refused or failed to co-operate ($n = 44$), or because the patient's file could not be found ($n = 29$) or because the reporting physician did not consider the admission as relevant to this study ($n = 2$).

The Audit Committee classified the remaining 727 discharge summaries as 'anaphylaxis probable' ($n = 155$), 'anaphylaxis possible' ($n = 238$), 'anaphylaxis unlikely' ($n = 309$) and as 'admission unclassifiable' ($n = 27$). A total of 632 admissions consisted of reactions which occurred outside the hospital and which were the direct reason for admission (community acquired). The remaining 95 consisted either of reactions in the outpatient clinic ($n = 58$) or inside the clinic during admission ($n = 24$) or of reactions on something which was bought or encountered outside The Netherlands and therefore could not be related to drug dispensing data inside The Netherlands ($n = 3$). The place of reaction was not mentioned in the remaining discharge summaries ($n = 10$) and therefore this could not be used to distinguish those cases in which the reaction was the direct reason for admission from the others. Of the 632 reactions which were reason

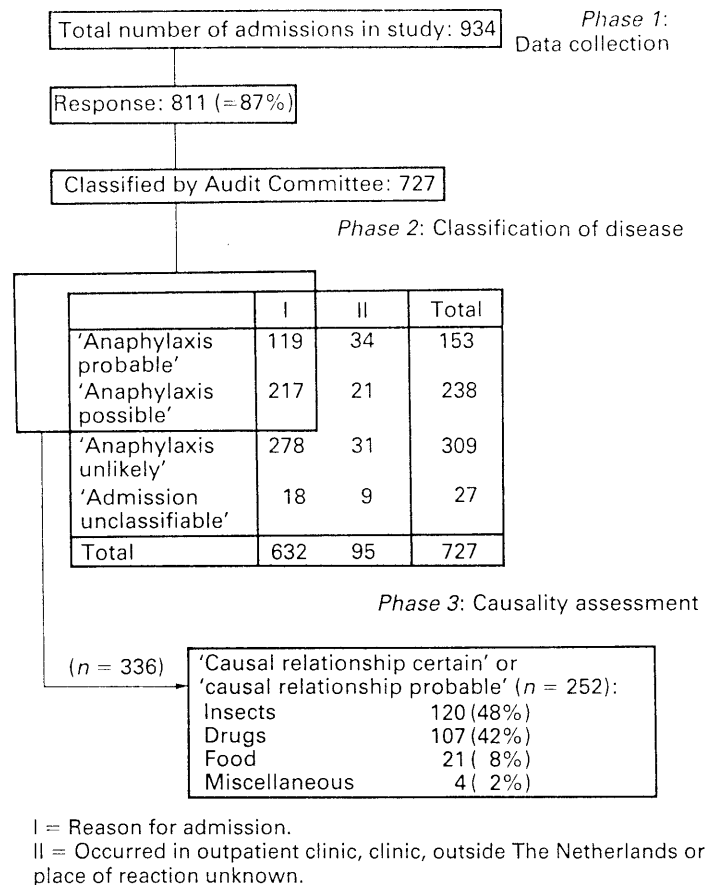


Figure 1 Overview of study results.

for admission, 119 were classified as 'anaphylaxis probable', 217 as 'anaphylaxis possible', 278 as 'anaphylaxis unlikely' and 18 as 'admission unclassifiable' (Figure 1).

Of the admissions coded as diagnoses 995.0 and 999.4, 25 (12%) were classified as 'anaphylaxis unlikely' by the Audit Committee. Some of these patients had been admitted with a reaction that was not anaphylaxis but, for example, a Herxheimer reaction, a toxic shock, an intoxication to a drug, collapse after use of nitroglycerin or convulsions. Two were diagnosed as hyperventilation. As a consequence, the definite false-positive misclassification was 12% in these groups. Out of categories 995.0 and 999.4, 174 admissions were classified as 'anaphylaxis probable' or 'anaphylaxis possible' (85% of the analysed admissions of these diagnosis categories). Of the cases classified as 'anaphylaxis probable', 69 came out of the 522 admissions from the other diagnosis categories, mainly from category 989.5 (venom; insect stings/bites). This makes the definite false-negative misclassification 13% in these categories. If category 989.5 was excluded, the false-negative misclassification was only 4% (15 cases out of 356 admissions of which data were received and which were classified by the Audit Committee).

Weighted kappa was reasonably high and remained that way throughout the study (0.55–0.77), which means that the agreement on classification was satisfactory and that the members of the Audit Committee were consistent in their classification.

In the total study there were four deaths: one patient died of a toxic shock, one during a catheter procedure in

order to remove stones from the choledochal duct and two patients died of anaphylaxis to intravenously administered contrast media. There were also 21 cases of non-fatal anaphylaxis due to contrast-media.

Only the reactions which occurred outside the hospital and led to admission and which were classified as 'anaphylaxis probable' or 'anaphylaxis possible' are used in the further analysis. This group consisted of 336 cases, 158 men and 178 women with a median age of 42.5 years (mean 41.0, range 2–84 years, s.d. 20.4) and 46.5 years (mean 44.9, range 1–90 years, s.d. 21.5) respectively. Symptoms recorded in the discharge summaries are summarized in Table 1.

In 252 of the 336 admitted cases classified as 'anaphylaxis probable' or 'anaphylaxis possible' the suspected agent had been classified as 'causal relationship certain' or 'causal relationship probable'. In those 252, an insect was the cause in 120 cases, a drug in 107 cases, food in 21 cases and in 4 cases it was something else such as a cleaning agent, a burst echinococcus cyst, or exercise-induced anaphylaxis (Table 2).

Of the above mentioned 107 drug-induced cases, glafenine was 20 times the causative agent (19%), amoxycillin 12 times (11%), diclofenac 8 times (7%) and combination preparations with paracetamol 7 times (7%) (of which in 6 cases (6%) propyphenazone was included in the preparation) (Table 2). There were no patients admitted more than once because of drug-induced anaphylaxis during the study-period.

Of the 107 cases 8 (7%) had been reported to The Netherlands Centre for Monitoring of Adverse Reactions to Drugs as cases of suspected drug-induced

Table 1 Symptoms* of 336 patients admitted because of anaphylaxis ('Anaphylaxis probable' ($n = 119$) and 'Anaphylaxis possible' ($n = 217$))

Symptoms	'Anaphylaxis probable'	'Anaphylaxis possible'	Total
Erythema	76 (64%)	115 (53%)	191 (57%)
Angioedema	65 (55%)	107 (49%)	172 (51%)
Hypotension	66 (55%)	56 (26%)	122 (36%)
Bronchospasm	61 (51%)	57 (26%)	118 (35%)
Pruritus	40 (34%)	77 (35%)	117 (35%)
Urticaria	34 (29%)	71 (33%)	105 (31%)
Collapse	42 (35%)	45 (21%)	87 (26%)
Nausea/vomiting	23 (19%)	43 (20%)	66 (20%)
Tachycardia	29 (24%)	34 (16%)	63 (19%)
Loss of consciousness	24 (20%)	22 (10%)	46 (14%)
Diarrhoea	6 (5%)	17 (8%)	23 (7%)
Upper airways†	12 (10%)	9 (4%)	21 (6%)
Conjunctivitis	12 (10%)	9 (4%)	21 (6%)
Laryngeal oedema	8 (7%)	11 (5%)	19 (6%)
Abdominal pain	7 (6%)	12 (6%)	19 (6%)
Bradycardia	11 (9%)	4 (2%)	15 (4%)

*There were also 13 patients in the group 'anaphylaxis probable' and nine patients in the group 'anaphylaxis possible' with symptoms of cardiac and/or cerebral ischaemia, one of them needing mechanical ventilation.

†Rhinitis, oedema of the uvula or pharynx.

Table 2 Causes of anaphylaxis leading to admission with a 'causal relationship certain' or a 'causal relationship probable'

	'Anaphylaxis probable'	'Anaphylaxis possible'	Total
Insects	63	57	120
Food	10	11	21
<i>Drugs</i>			
Glafenine	12	8	20
Amoxycillin	6	6	12
Diclofenac	2	6	8
Analgesics with paracetamol (including propyphenazone)	5	2	7
Enalapril	—	4	4
Co-trimoxazole	—	4	4
Dipyrene	1	2	3
Nitrofurantoin	1	2	3
Carbaspirin calcium	1	2	3
Desensitization agents	1	2	3
Amoxycillin + clavulanic acid	—	3	3
Phenethicillin potassium	1	1	2
Nifurtinol	—	2	2
Trimethoprim	—	2	2
Naproxen	—	2	2
Aspirin	—	2	2
Miscellaneous drugs (all mentioned once)	10	17	27
Other causes	1	3	4
Total	114	138	252

anaphylaxis, as was determined by comparing birth date, gender and date of admission in both files.

Table 3 shows the absolute number of anaphylactic reactions per drug or drug group and the risks of anaphylaxis, relative to the total number of prescriptions in 1987 and 1988 separately. Although there is variation per year and per probability class A–C, the point estimates of the relative risks of anaphylaxis to glafenine, amoxycillins, diclofenac, penicillins and analgesics are invariably distinctly greater than one in the group 'anaphylaxis probable'. The lower relative risks in the groups including cases classified as 'anaphylaxis possible' (B and C) may be attributed to

non-differential misclassification of disease (Rothman, 1986). The latter resulted from the fact that the group 'anaphylaxis possible' included cases in which anaphylaxis could not be excluded but was not very likely either (e.g. ninth-day rash to amoxycillin). Therefore, we concentrated our analysis on the group 'anaphylaxis probable'. The drug with the highest relative risks was glafenine. In order to assess the risk relative to other well-known causes of anaphylaxis, glafenine was compared with drugs that had been the causative agent of anaphylaxis more than four times in this study. Glafenine was also compared with the group of antiinflammatory and antirheumatic drugs (NSAID),

Table 3 Relative risks of glafenine, diclofenac, amoxycillins, analgesics, penicillins and NSAID vs all other drugs in 1987 and 1988

Drug class (ATC-code in brackets)	Prescriptions	Anaphylaxis hospitalizations			RR (CI 95%) (Drug induced)		
	1987	1987					
	(n = 562, 855)	A	B	C			
Glafenine (N02BG03)	1667	6	6	12			
Amoxycillins (J01CA04, J01CA54)	10410	4	5	9			
Analgesics with paracetamol (N02BE01, N02BE51, N02BE71)	20062	3	1	4			
Diclofenac (M01AB05)	7471	0	1	1			
Penicillins (J01C, J01H, J01J)	14624	4	5	9			
NSAID (M01AA, M01AB, M01AE)	21223	2	2	4			
Analgesics (N02BA, N02BB, N02BE)	27403	4	3	7			
	1988	1988					
	(n = 832, 856)	A	B	C			
Glafenine (N02BG03)	2415	6	2	8			
Amoxycillins (J01CA04, J01CA54)	18412	2	1	3			
Analgesics with paracetamol (N02BE01, N02BE51, N02BE71)	30379	2	1	3			
Diclofenac (M01AB05)	13423	2	5	7			
Penicillins (J01C, J01H, J01J)	25403	3	8	11			
NSAID (M01AA, M01AB, M01AE)	34322	3	6	9			
Analgesics (N02BA, N02BB, N02BE)	42683	6	4	10			
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CI 95% = Confidence Interval 95% calculated according to Miettinen (1982).

Table 4 Relative risk in the group 'anaphylaxis probable' (glafenine vs control drug, 1987 and 1988), estimated on the basis of the number of prescriptions and exposed patients

<i>Glafenine/Control drug</i>	<i>Relative risk (+ 95%-confidence limits)</i>	
	<i>Prescriptions</i>	<i>Exposed patients</i>
Glafenine/Analgesics with paracetamol	24.7 (12.8 < RR < 47.8)	24.7 (12.8 < RR < 47.7)
Glafenine/Diclofenac	30.7 (11.8 < RR < 79.9)	29.6 (11.3 < RR < 77.7)
Glafenine/NSAID	32.7 (16.9 < RR < 63.0)	26.0 (13.0 < RR < 52.0)
Glafenine/Salicylic acid and derivatives, including combinations	27.7 (10.4 < RR < 73.9)	27.0 (10.1 < RR < 72.3)
Glafenine/Analgesics	20.6 (11.5 < RR < 37.1)	18.6 (10.2 < RR < 33.9)

with salicylic acid and its derivatives and, since it is a non-narcotic analgesic, with the total group of non-narcotic analgesics except, of course, for glafenine (Table 4). The relative risk estimation was made on the basis of prescriptions and numbers of patients in the 2-year period 1987–1988. Use of glafenine had the highest risk of anaphylaxis in all analyses. When comparing glafenine with combination preparations containing paracetamol the point estimator of the relative risk was (prescriptions and exposed patients respectively) 24.7 – 24.7, with diclofenac 30.7 – 29.6, with NSAID 32.7 – 26.0, with salicylic acid and derivatives 27.7 – 27.0 and with analgesics 20.6 – 18.6. Analysis on the basis of days at risk gave similar figures as analysis on the basis of prescriptions and exposed patients. We also made a comparison with penicillins, since penicillins have a well-known and well evaluated risk of anaphylaxis. This gave rise to a relative risk of 16.8 ($8.5 < RR < 33.3$) (prescriptions) and 20.0 ($10.4 < RR < 38.6$) (exposed patients).

Discussion

This study shows that drugs and insect stings were by far the most important cause of admission because of anaphylaxis in The Netherlands in 1987 and 1988. Glafenine, amoxycillins and diclofenac were the three most important causes of admission because of drug-induced anaphylaxis. Although there were also 23 cases of contrast-media-induced anaphylaxis, these occurred during admission or in the outpatient clinic, and hence these could not be related to the drug dispensing data from community pharmacies.

For this study we considered several types of epidemiological design. Because of the low incidence of anaphylaxis, we did not consider a cohort study as a useful approach. Case-control studies are very suitable for studying rare diseases and are often used when a relationship between the adverse event and a drug is uncertain. In the case of anaphylaxis, however, the temporal relationship and clinical pattern usually leave little doubt concerning the causal relationship. We had several reasons for not using a case-control design. Firstly, recall bias would have been introduced into the study. As anaphylaxis is a rapidly developing and impressive type of reaction that patients are not likely

to forget, it would not have been easy to find controls subject to the same recall of exposure as cases. Secondly, as drugs are a well-known cause of anaphylaxis, physicians might inquire more insistently about drug use in the index than in the control group. Thirdly, although anaphylaxis is considered to be a rare disease, the low population exposure prevalence of some drugs (e.g. glafenine) could consequently have meant that none of the controls would have been exposed to those drugs. Therefore, we used a case-cohort design, in which the cases were all patients admitted because of anaphylaxis in The Netherlands in 1987 and 1988 and the control cohort was a reference cohort of the Dutch population.

Theoretically, our analysis could have been adversely influenced by three issues. Firstly, diagnostic suspicion bias or referral bias could have played a role. Because of the characteristic pattern and temporal relationship however, and irrespective of the causative agent, anaphylaxis is mostly recognized. It is highly unlikely that general practitioners would recognize anaphylaxis to one drug (e.g. diclofenac) more easily than that to another (e.g. glafenine). Similarly, general practitioners decide on admission of their patients to the hospital on the basis of severity instead of cause. Hence it is unlikely that they would tend to admit more patients with anaphylaxis to one particular type of exposure. This brings us to the second issue: in this study cases of anaphylaxis that were not admitted to a hospital were not included. This could mean that, if anaphylaxis to one drug was more severe than anaphylaxis to another, patients with anaphylaxis to such a drug would have been admitted relatively more often than patients with anaphylaxis to other drugs. However, there are no reasons to believe that anaphylaxis to orally administered amoxycillin, diclofenac or glafenine has a worse prognosis than anaphylaxis to other orally administered drugs. Hence, this will mean that the proportion of community acquired cases of anaphylaxis which leads to admission is more or less the same for these drugs. Thirdly, the reference cohort was not a random sample from the total study base. Random samples are, however, not a goal in themselves but used to ensure that the exposure data are representative of the total study base. It is logistically impossible to take a random sample from the total study base of all inhabitants in The Netherlands. Instead of this we used a representative sample of community

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pharmacies, located in different parts of the country. Therefore, differences in prescribing by medical practitioners in different parts of the country played no role. Thus, we are not aware of any reasons to suggest that the exposure in the reference cohort differs substantially from the exposure in the total study base, especially not as the vital statistics concerning age and gender of the reference cohort were the same as that of the population in The Netherlands.

This study was restricted to principal diagnoses and thus no additional diagnoses have been analysed. The reason is that reporting of additional diagnoses is voluntary. This means that the reporting of additional diagnoses varies per hospital, and it is unknown what percentage of the additional diagnoses is reported. For this reason, in this study the cases of anaphylaxis that occurred inside the hospital were not included. Moreover, the dispensing data from hospital pharmacies are rarely registered on an individual patient level.

The most valid relative risk estimations were made with the group 'anaphylaxis probable'. This is obvious, in view of the fact that the group 'anaphylaxis possible' comprised many non-anaphylactic hypersensitivity reactions. Hence, this introduced a misclassification bias towards a relative risk of one in the combined group of 'anaphylaxis possible' and 'anaphylaxis probable' (Rothman, 1986) (Table 3).

Of the group 'anaphylaxis probable' 117 out of 119 cases were considered severe on the grounds of involvement of the cardiovascular and/or the respiratory system. For the same reason, of the group 'anaphylaxis possible' 125 out of 217 were considered severe. Re-analysis with severe cases did not substantially alter the relative risk comparisons between the drugs. Moreover, since every case in this group has led to a hospital admission, every case should be considered as severe.

The current study confirms the results of an earlier one (Stricker *et al.*, 1991) of a different design. In the current study, besides all cases classified as anaphylaxis, a random sample of cases with other diagnoses was investigated, in order to assess false-negative misclassification. Secondly, all cases were analysed by a blinded Audit Committee in order to prevent classification bias due to knowledge of the cause. Thirdly, relative risk estimations were made with drug dispensing data instead of reimbursement figures from health insurance funds. The former more accurately reflect the consumption of drugs as dis-

persing data are available on an individual level and as all socio-economic groups are included.

In the current study more cases of anaphylaxis to insect stings were recorded, largely due to the fact that diagnosis code 989.5 (venom: insect stings/bites) was included. The highest risk of community acquired drug-induced anaphylaxis was recorded for the individual agents glafenine, amoxycillin and diclofenac. The risk of anaphylaxis to glafenine relative to penicillins was consistent with the results of the previous study. In the previous study, however, no cases of anaphylaxis to amoxycillin and diclofenac were recorded.

In the absence of reliable outpatient diagnoses this study yields no incidence figures. As the risk of anaphylaxis to penicillins has been estimated at approximately 1:10,000 prescriptions (Brown *et al.*, 1961; Saxon *et al.*, 1987; Weiss & Adkinson, 1988), and the lower 95% confidence limit of the relative risk vs this group varies from 5 to 10 in the series of analyses, the incidence of anaphylaxis to glafenine may be estimated at 1:1,000 to 1:2,000 prescriptions and hence of diclofenac at approximately 1:10,000 to 1:20,000.

Partly based on the current study, the Committee on Proprietary Medicinal Products (CPMP) of the European Community decided to issue a negative opinion on glafenine, which was supported by 10 of the 12 member states (Anonymous, 1992). This advice has been followed by the withdrawal of glafenine in several countries (e.g. The Netherlands, Spain).

We conclude that the case-cohort design—as employed in our study—may be useful for postmarketing surveillance. Unlike a traditional case-control study which requires the enrolment and exposure assessment of controls for every study, the sample cohort of a case-cohort study may be used as a reference for several post-marketing surveillance studies. Moreover, a case-cohort design is suitable for studying rare events to rare exposure. This could make the case-cohort design useful for studying new adverse events in the first two years of marketing of drugs which still have a low exposure prevalence.

Audit Committee: the Audit Committee consisted of the consultants in internal medicine K-H. Brandt, L. Kuenen and J. Roos.

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