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Fluoroquinolone-Associated Anaphylaxis in Spontaneous Adverse Drug Reaction Reports in Germany

Differences in Reporting Rates Between Individual Fluoroquinolones and Occurrence after First-Ever Use

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Abstract

Background: The frequency of fluoroquinolone-associated anaphylaxis has been estimated to be 1.8–23 per 10 million days of treatment based on spontaneous reports. It is unknown whether there are differences between the reporting rates of anaphylaxis with individual fluoroquinolones. According to pathophysiology, anaphylaxis may be immune mediated (anaphylactic) or not (anaphylactoid). The latter may occur after first-ever intake since no sensitisation phase is necessary.
Objective: To analyse spontaneous reports of fluoroquinolone-associated anaphylaxis contained in the spontaneous adverse drug reaction database of the Federal Institute for Drugs and Medical Devices in Germany with regard to differences in reporting rates between various fluoroquinolones, the previous intake and the time to onset of the reaction.
Methods: All fluoroquinolone-associated cases of anaphylaxis, anaphylactic shock, and anaphylactic/anaphylactoid reaction spontaneously reported to the Federal Institute for Drugs and Medical Devices between 1 January 1993 and 31 December 2004 were identified and assessed with regard to the correctness of the diagnosis of anaphylaxis, the causal relationship with the drug, the previous intake of fluoroquinolones and the time to onset of the reaction.
Results: In 166 of 204 cases identified, the diagnosis of anaphylaxis and a causal relationship with the drug were considered at least possible. Moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin accounted for 90 (54%), 25 (15%), 21 (13%) and 16 (10%) of the 166 cases, respectively. The corresponding reporting rates per 1 million defined daily doses based on crude estimates of exposure were 3.3, 0.6, 0.2 and 0.2 for moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin, respectively. The occurrence of anaphylaxis after the first dose or within the first three days was reported in 71 of 166 (43%) cases, but no information on prior exposure with this or any other fluoroquinolone was provided with these reports. In 21 of 166 (13%) cases, the reaction occurred within the first 3 days and it was stated that the particular fluoroquinolone had never been taken before.
Conclusions: Anaphylaxis appears to be associated with the fluoroquinolone class of antibacterials. Observed differences in reporting rates should be further

investigated. Fluoroquinolone-associated anaphylaxis may occur after first-ever intake of the agent.

Background

The fluoroquinolones are widely used synthetic antibiotics with a potent antibacterial effect against Gram-positive and Gram-negative bacteria. As a class, the fluoroquinolones are considered generally well tolerated and safe.[1,2] The adverse drug reactions (ADRs) associated with their intake most commonly affect the gastrointestinal system, CNS and skin.[1,3] Common hypersensitivity reactions to fluoroquinolones (i.e. rash) have been observed in clinical trials and were recognised as the most frequently reported reactions to fluoroquinolones in an analysis of spontaneous reports in Italy.[4] However, more severe reactions, such as anaphylaxis, have not been observed in clinical trials and first became apparent in spontaneous and literature reports after the marketing of these drugs.[2,3] Ciprofloxacin, for instance, received marketing authorisation in the US in 1987. By 1988 a total of 15 cases of anaphylaxis or anaphylactoid reactions associated with ciprofloxacin use had been received by the US FDA.[5]

Interestingly, in a considerable number of cases, anaphylaxis was reported to occur after the first intake of a particular fluoroquinolone.[5] According to pathophysiology, anaphylaxis may either be immune (IgE)-mediated or non-immune-mediated, e.g. by direct stimulation of the effector cells. Both mechanisms produce the same clinical picture; however, non-immune-mediated reactions may occur after first-ever intake, as no sensitisation phase is necessary. For the sake of differentiation, non-immune-mediated reactions were formerly also referred to as anaphylactoid reactions, in contrast to the IgE-mediated anaphylactic reactions.[6,7]

The clarification of the underlying pathomechanism in fluoroquinolone-associated immediate reactions has proven difficult since there is no routine test for the detection of fluoroquinolone-specific IgE and skin tests have been found to both be negative in affected individuals and to elicit positive reactions in healthy control subjects.[2,8] These false positive reactions were probably triggered by the known direct histamine release induced by fluoroquinolones.[2]

Based on spontaneous ADR reports, the frequency of fluoroquinolone-associated anaphylaxis has been estimated to be 1.8–23 per 10 million days of treatment, depending on the fluoroquinolone studied.[9] Other publications, using the terms 'anaphylaxis/anaphylactoid reaction', have reported such reactions to occur after ciprofloxacin in 1.2 per 100 000 prescriptions.[5] The total number of cases of anaphylaxis could gain considerable impact if the exposure to fluoroquinolones were to rise abruptly, for instance, in certain scenarios of bioterrorism.[3]

However, it is currently unknown whether the various fluoroquinolones are associated with different individual occurrence and reporting rates for anaphylaxis. In addition, different terms used in various investigations, e.g. 'anaphylaxis', 'anaphylactic shock', 'anaphylactic/anaphylactoid reaction', hamper such comparisons.

In Germany, a large number of cases of suspected serious ADRs are reported spontaneously to the competent authority, the Federal Institute for Drugs and Medical Devices (BfArM), where they are assessed and registered in a large ADR database. The main aim of the spontaneous reporting system is to detect previously unknown ADRs or those occurring in a quantitatively or qualitatively different manner from that expected.[7,10]

However, analysis based on spontaneous ADR reports have several principal limitations[7] and are subject to various biases, as has been learnt in the past.[11] The cases that are spontaneously reported may not be representative and, with regard to the quantity, are only part of the total cases that occur with this drug (so-called under-reporting). The size of this under-reporting cannot accurately be determined. In two studies investigating drug-induced anaphylaxis on the basis of spontaneous ADR reports, only 4% and 8% of cases, respectively, had been reported to the competent regulatory authority.[12]

Conversely, spontaneous ADR reporting may also be stimulated by several factors (so-called over-

reporting), including special efforts by medical bodies or competent authorities, literature reports or active retrieval of ADR reports by the pharmaceutical company representatives during their regular contacts with physicians prescribing the drug.[13] Despite these limitations, analysis of spontaneous ADR reports has been proven appropriate and helpful in detecting unexpected and unpredictable type B effects, such as drug-induced anaphylaxis, which cannot be recognised in clinical studies since they occur only in a minority of patients.[7,10] In addition, calculations of proportional reporting ratios (PRRs) have been described to further refine signal generation based on spontaneous reports.[14] For these reasons, analysis of spontaneous ADR reports and calculation of PRRs have been chosen as the methodological tools for this investigation.

Objective

The objective of the present study was to analyse the ADR reports of fluoroquinolone-associated anaphylaxis for the period 1993–2004 contained in the BfArM ADR database with regard to (i) differences in the reporting rates between various fluoroquinolones; and (ii) the previous intake of fluoroquinolones and time to onset of reaction (under the assumption that no sensitisation phase is necessary for non-immune-mediated reactions).

Methods

Setting, Reporting Sources and Database

In Germany, physicians and pharmacists are obliged by their professional code of conduct to report suspected serious ADRs to their professional councils, who forward these reports to the BfArM. A considerable number of reported cases received by the BfArM also stem from the pharmaceutical industry, which is obliged to report, within 15 days, any serious ADR associated with the administration of their drugs that they have been notified about. A small number of cases are reported directly by consumers; however, they have to be confirmed by a healthcare professional. Hence, the BfArM covers the whole country with regard to the reporting of ADRs. All of these reports are assessed by pharmacovigilance professionals and stored in the BfArM ADR database. Data concerning suspected ADRs and the drugs involved are coded using the WHO adverse reaction terminology (WHO-ART) and the Anatomical Therapeutic Chemical (ATC) classification system, respectively. The investigators of the present study did not contact the original reporter of the ADR in any of the cases.

Case Identification

A two-stage approach for the identification and confirmation of cases, as has also been performed in similar investigations, was employed.[12,15,16] First, to ensure that cases are not missed, all fluoroquinolone-associated (ATC code J01ma) reactions that were coded with the WHO-ART terms ‘anaphylaxis’, ‘anaphylactic shock’ and ‘anaphylactic/anaphylactoid reaction’ and that were registered between 1 January 1993 and 31 December 2004 were identified in the database. Spontaneous reports resulting from postmarketing studies were excluded.

In the second phase, all the cases identified were assessed with regard to the correctness of the diagnosis of anaphylaxis and the causal relationship with the incriminated drug. In further analysis, only cases in which the diagnosis of anaphylaxis and the causal relationship with the intake of the drug were assessed as being at least possible were considered.

Assessment of Cases with Regard to the Diagnosis Anaphylaxis

Anaphylaxis is defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.[17] The diagnosis of anaphylaxis was assessed according to an internationally agreed algorithm as described in detail elsewhere.[15,16] Cases were excluded for any of the following reasons: acute myocardial infarction, acute pulmonary embolism, acute major haemorrhage and acute septicaemia. The categories applied with regard to the correctness of the diagnosis anaphylaxis were as follows: certain, probable, possible, unlikely and not classifiable.

Considering the nature of the data, e.g. spontaneous reports, it was acknowledged that, in some reports, the physicians presumably already had transferred the symptoms observed into a diagnosis, i.e. anaphylaxis, thus only stating this diagnosis in the ADR report but not every symptom observed.

Hence, in these reports the aforementioned algorithm could not be applied. However, anaphylaxis could still be considered possible in those cases where patients were treated with intravenously administered sympathomimetic amines, corticosteroids or antihistamines, or in cases where referral to a hospital or within a hospital to an intensive care unit was necessary. These 37 cases were coded separately as 'anaphylaxis'.

Assessment of Cases with Regard to the Causal Relationship

All cases identified were also assessed with regard to the assumed causal relationship between the observed reaction and the drug(s) that had been taken based on criteria used by the WHO drug monitoring centre.[18] The categories applied were certain, probable, possible, unlikely and unclassifiable.

Assessment of Previous Fluoroquinolone Intake and Time to Onset

In addition, all cases were classified according to the previous history of fluoroquinolone intake and the time to onset of the reaction. The intention was to gather data that would suggest immune-mediated or non-immune-mediated reactions, under the assumption that non-immune-mediated reactions may occur after first-ever intake, since no sensitisation phase is necessary.

Identification of Non-Anaphylaxis Cases with Circulatory and Respiratory Symptoms

For the identification of cases of fluoroquinolone-associated circulatory and respiratory symptoms that were not reported as anaphylaxis, spontaneous ADR reports received by the BfArM during the same period (1 January 1993–31 December 2004), excluding the terms 'anaphylaxis', 'anaphylactic shock' and 'anaphylactic/anaphylactoid reaction' but coded with the WHO-ART terms 'circulatory failure', 'circulatory shock', 'shock', and 'bronchospasm'; and 'bronchospasm aggravated', 'dyspnoea', 'laryngeal oedema' and 'throat tightness', respectively, were identified. Cases originating from postmarketing studies were excluded.

Proportional Reporting Rate (PRR)

The PRR is a statistical aid to signal generation that utilises the stability of a large database. The PRR involves calculation of the proportions of specified reactions for a drug of interest, where the comparator is all other drugs in the database.[14] The expected or null value for a PRR is one and the values generated are measures related to the strength of the association that behave in a fashion similar to a relative risk (the higher the PRR, the greater the strength of the signal).

In this study, reference was not made to all other drugs, but to the class of drugs, i.e. the other fluoroquinolones. In addition, the total number of cases of anaphylaxis was considered instead of the total number of reactions of interest, due to the fact that a particular ADR was not investigated, but rather a condition defined by different symptoms and possibly summarised by different terms. The PRR is calculated as $a/(a + c)$ divided by $b/(b + d)$ in a two-by-two table (see figure 1). In the present analysis, cumulative PRRs are shown, i.e the data used for the calculation of the PRR for each successive year is added to the previous total and so on. Accordingly, for each fluoroquinolone the cumulative PRR for 2004 represents the total value over all years since the year in which the drug first received marketing authorisation.

Since PRR values can be subjected to statistical analysis,[14] chi-squared tests were performed. The wording "significantly increased PRR", as used in the text, refers to a PRR-value ≥ 2, with a p-value <0.05 and where the lower limit of the 95% confidence interval exceeds 1. The judgement about whether PRR-values suggest a signal was made on the basis of the PRR value itself (≥ 2), the confidence interval around the PRR, the absolute number of anaphylaxis reports for the fluoroquinolone of interest (≥ 3)[14] and the consistency of the observation over a longer time period (≥ 3 years).

For the PRR calculations, all cases that were coded with the WHO-ART terms 'anaphylaxis', 'anaphylactic shock' and 'anaphylactic/anaphylactoid reaction' and that were spontaneously reported to the BfArM, excluding reports from postmarketing studies, were taken into account without prior as-

	Fluoroquinolone of interest	All other fluoroquinolones
Cases coded as anaphylaxis, anaphylactic shock and anaphylactic/ anaphylactoid reaction	a	b
All other cases	c	d
Total	a + c	b + d

$$PRR = \frac{a/(a + c)}{b/(b + d)}$$

Fig. 1. Two-by-two contigency table used for the calculation of proportional reporting rates (PRRs).[11,14]

sessment of the correctness of the diagnosis and causal relationship with the incriminated drug.

In order to address differential reporting due to different dates of marketing authorisation, PRRs were calculated for fluoroquinolones from the individual date of marketing authorisation in Germany up until 2004. PRRs were only calculated for fluoroquinolones with a cumulative total of >5 anaphylaxis reports.

Exposure Data and Date of Marketing in Germany

For the purpose of estimating the exposure of patients to the different fluoroquinolones available in Germany during the period 1 January 1993–31 December 2004, reference was made to published utilisation data that have known limitations,[19] as they only capture the outpatient fluoroquinolone prescriptions that are reimbursed by the compulsory health insurances in Germany. However, the exposure to fluoroquinolones in hospitals may only account for a minor part of the total fluoroquinolone-exposure and the lack of consideration of hospital fluoroquinolone administration applies for all the fluoroquinolones. Although the exposure data used do not include prescription data from patients exempted from the compulsory health insurances in Germany, such exemptions only apply to approximately 10% of the German population[20] and again, this lack of consideration applies for all the fluoroquinolones.

The date of marketing authorisation in Germany for the selected fluoroquinolones was May 1985 for ofloxacin, January 1987 for ciprofloxacin, January 1998 for levofloxacin and June 1999 for moxifloxacin.

Analysis of the WHO Database

The WHO database was searched for the number of reports of anaphylaxis (high-level search term according to WHO-ART: 'anaphylactic reaction') associated with moxifloxacin and the total number of reports of anaphylaxis associated with all other fluoroquinolones for the period 1999 (date of international marketing authorisation for moxifloxacin: June 1999) to December 2004 (data lock point).

Results

A total of 204 fluoroquinolone-associated cases of anaphylaxis, anaphylactic shock, anaphylactic/ anaphylactoid reaction (summarised for brevity as anaphylaxis) reported to the BfArM between 1 January 1993 and 31 December 2004 were identified in the ADR database and were assessed with regard to the correctness of the diagnosis of anaphylaxis and the causal relationship with fluoroquinolone intake. Figure 2a and figure 2b provide a breakdown of these two assessments for the individual fluoroquinolones and for all of the fluoroquinolones combined. Further analyses were restricted to the 166 reports in which the diagnosis of anaphylaxis and the causal relationship with the intake of the drug were both assessed as being at least 'possible'.

Age, Sex and HIV Infection

The sex of the affected patient was given as being female in 91 of 166 (55%) reports and as being male in 67 of 166 (40%) reports. No information on sex was provided in 8 of 166 (5%) reports. Most reports involved patients aged 20–49 years (93 of 166; 56%). There was no appropriate information on age in 20 of 166 (12%) reports. Among the 166 reports, three (2%), had a fatal outcome.

The route of administration of the fluoroquinolone was described as being oral in 160 of 166 (96%) reports and as intravenous in 5 of 166 (3%)

reports. In the remaining report, no information on the route of administration was provided.

The ADR reports originated mostly from general practitioners (66 of 166; 40%), hospitals (28 of 166; 17%) and specialists (20 of 166; 12%). No information concerning the profession of the reporter of the ADR was provided in 52 of 166 (31%) reports.

Underlying HIV infection was not reported in any of the 166 cases.

Differences in Reporting Rates

Moxifloxacin accounted for 90 of 166 (54%) reports of possible fluoroquinolone-related anaphylaxis and this finding was not reflected by an excessive exposure (26.9 million defined daily doses [DDD]) compared with the other fluoroquinolones. Levofloxacin accounted for 25 of 166 (15%; 40.3 million DDD) reports of possible fluoroquinolone-related anaphylaxis, ciprofloxacin for 21 of 166 (13%; 98.5 million DDD) and ofloxacin for 16/166 (10%; 74.2 million DDD). The intake of other fluoroquinolones was reported in 14 of 166 (8%)

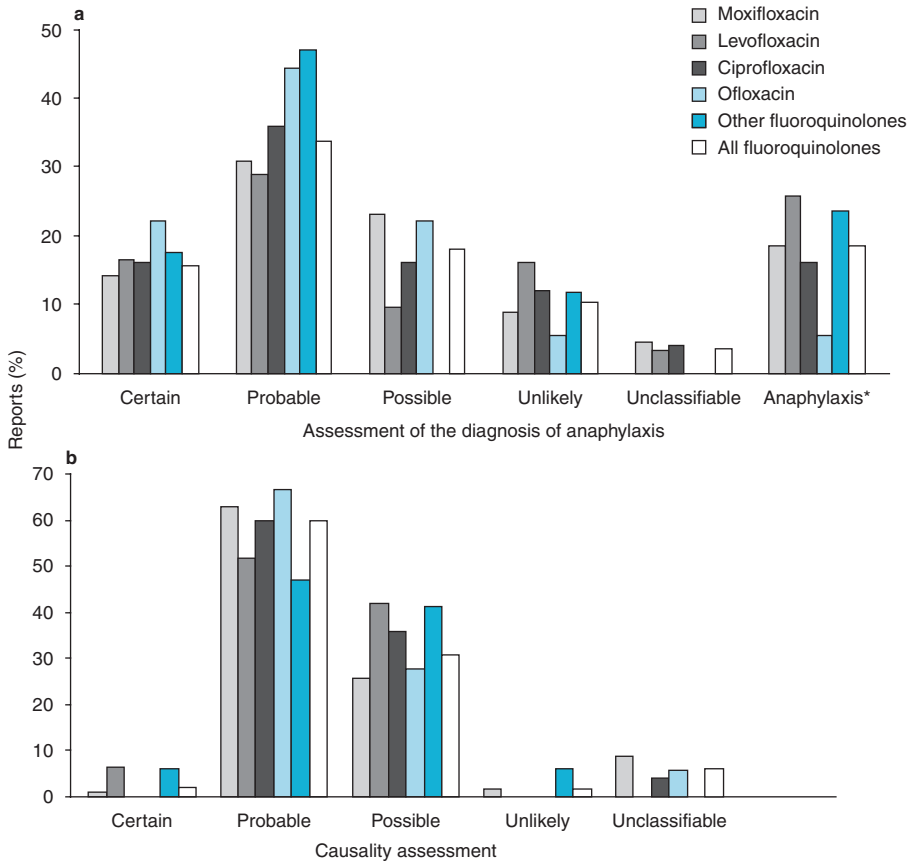

Fig. 2. Assessment with regard to the correctness of diagnosis (**a**) and the causal relationship with the incriminated drug (**b**) in the 204 fluoroquinolone-associated cases of anaphylaxis reported to the Federal Institute for Drugs and Medical Devices as anaphylaxis, anaphylactic shock and anaphylactic/anaphylactoid reaction in the period from 1 January 1993–31 December 2004. The cases per individual fluoroquinolone that were in each of the different correctness and causality categories, respectively, are expressed as the percentage of the total of cases for this agent. Only fluoroquinolones with a cumulative total of more than five cases in the period under consideration are depicted separately. **Anaphylaxis*** = anaphylaxis stated in the report but no information, e.g. on blood pressure or respiratory symptoms, was given. However, anaphylaxis could be considered as possible provided that certain criteria were met (see Methods section).

reports. The corresponding reporting rates per 1 million DDD were 3.3, 0.6, 0.2 and 0.2 for moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin, respectively (figure 3).

PRRs

In order to address differential reporting due to different times of marketing authorisation, cumulative PRRs were calculated for all anaphylaxis cases reported spontaneously to the BfArM, not only for the entire period from 1993 to 2004, but also for the time since the marketing authorisation of the individual fluoroquinolone in Germany until 2004 (table I). PRRs were significantly increased for moxifloxacin for a consecutive period of 4 years (2001–2004). For ofloxacin, one significantly increased PRR of 7.5 was calculated in 1986. However, this should be interpreted with caution because of the low number of reports of anaphylaxis for other fluoroquinolones, resulting in a wide confidence interval (95% CI 1.76, 31.96). In addition, non-significantly increased cumulative PRRs (≥2) were found for moxifloxacin in the year 1999 (2.1), for ofloxacin in the year 1987 (2.3), for ciprofloxacin in the year 1988 (2.3) and for levofloxacin in the year 1998 (2.0).

Circulatory or Respiratory Symptoms Not Reported as Anaphylaxis

To address possible reporting of anaphylaxis as diagnoses defined by different symptoms, cases with circulatory or respiratory symptoms that were not reported as anaphylaxis were identified in the BfArM database for the same period as were the reports of anaphylaxis (1 January 1993–31 December 2004) [figure 4]. Moxifloxacin accounted for 42% and 40% of these reports, respectively.

Reports of Anaphylaxis and of All Other Adverse Drug Reactions Per Year

Figure 5 shows the number of spontaneous reports of anaphylaxis received by the BfArM for selected fluoroquinolones and all fluoroquinolones together for the period 1 January 1993–31 December 2004. The increase in the total number of cases of anaphylaxis associated with fluoroquinolones that has occurred since 2000 seems mainly to be driven by reports associated with moxifloxacin. In contrast, the total number of reports of ADRs associated with moxifloxacin appears to be broadly stable from 2000 to 2004 (figure 6).

WHO Database

In the WHO database, the number of reports of anaphylaxis associated with moxifloxacin has increased since 2000 (date of international marketing authorisation: June 1999). Since 2002, moxifloxacin has the highest number of reports of anaphylaxis among all fluoroquinolones (data lock point December 2004) [data not shown].

Time to Onset of Reaction and History of Previous Intake

Occurrence of anaphylaxis after the first dose or within the first 3 days of use was described in 71 of 166 (43%) reports, but no information on prior exposure with this or any other fluoroquinolone was provided in these reports or it was stated that the occurrence of prior exposure was unclear (figure 7). In 21 of 166 (13%) reports, anaphylaxis occurred after the first use or within the first 3 days of use, and it was stated that the respective fluoroquinolone had never been taken before, although previous administration of a different fluoroquinolone was not explicitly excluded. Hence, the latter constellations do not appear to be compatible with a primary immune response; however, a secondary immune response due to prior sensitisation to the respective or a different fluoroquinolone (based on a cross reaction) cannot be excluded. In 2 of 166 (1%) reports, anaphylaxis occurred after first use or within the first 3 days of use and it was stated explicitly that no fluoroquinolone had ever been taken before, suggesting non-immune-mediated mechanisms for the reaction in these two cases.

Discussion

In the present study we were able to demonstrate that anaphylaxis has been reported in association with the intake of various fluoroquinolones, which is suggestive of this being a class effect of these compounds. Moxifloxacin accounted for 54% of the cases during the study period where both the diagnosis of anaphylaxis and a causal relationship with the

Table I. Cumulative proportional reporting rates (PRRs) for cases of fluoroquinolone-associated anaphylaxis reported spontaneously to the Federal Institute for Drugs and Medical Devices[a]

Period ending	Proportion of ADRs that were anaphylaxis (%)		PRR		
year-end	individual fluoroquinolone (a/a + c)	all other fluoroquinolones (b/b + d)	point estimate	p-value	95% CI
Moxifloxacin					
1999	3/46 (6.52)	11/357 (3.08)	2.117	0.230	0.613, 7.308
2000	14/238 (5.88)	25/554 (4.51)	1.304	0.414	0.690, 2.463
2001	32/394 (8.12)	32/803 (3.99)	2.038	0.003	1.268, 3.277
2002	54/629 (8.59)	39/1087 (3.59)	2.393	<0.001	1.604, 3.570
2003	80/806 (9.93)	47/1277 (3.68)	2.697	<0.001	1.902, 3.824
2004	111/958 (11.59)	52/1438 (3.62)	3.204	<0.001	2.329, 4.408
Levofloxacin					
1998	5/61 (8.20)	8/196 (4.08)	2.008	0.200	0.682, 5.912
1999	11/211 (5.21)	16/449 (3.56)	1.463	0.318	0.691, 3.097
2000	19/307 (6.19)	33/742 (4.45)	1.392	0.237	0.804, 2.408
2001	23/433 (5.31)	54/1021 (5.29)	1.004	1.000	0.625, 1.615
2002	24/556 (4.32)	82/1417 (5.79)	0.746	0.193	0.478, 1.163
2003	27/640 (4.22)	111/1700 (6.53)	0.646	0.034	0.429, 0.974
2004	29/702 (4.13)	145/1951 (7.43)	0.556	0.002	0.377, 0.820
Ciprofloxacin					
1987	0/23 (0)	18/829 (2.17)	0.000	0.541	0.267, 13.793
1988	5/97 (5.15)	29/1274 (2.28)	2.264	0.079	0.897, 5.719
1989	6/182 (3.30)	33/1578 (2.09)	1.576	0.296	0.670, 3.711
1990	9/278 (3.24)	37/1760 (2.10)	1.540	0.236	0.752, 3.156
1991	10/322 (3.11)	39/1854 (2.10)	1.476	0.263	0.745, 2.928
1992	11/367 (3.0)	42/1942 (2.16)	1.386	0.327	0.720, 2.666
1993	12/413 (2.91)	43/2053 (2.09)	1.387	0.309	0.738, 2.608
1994	13/450 (2.89)	47/2124 (2.21)	1.306	0.388	0.712, 2.392
1995	15/513 (2.92)	49/2211 (2.22)	1.319	0.340	0.746, 2.334
1996	16/554 (2.89)	51/2297 (2.22)	1.301	0.352	0.748, 2.263
1997	18/607 (2.97)	58/2416 (2.40)	1.235	0.427	0.733, 2.080
1998	22/665 (3.31)	67/2615 (2.56)	1.291	0.262	0.804, 2.074
1999	23/721 (3.19)	80/2962 (2.70)	1.181	0.475	0.748, 1.864
2000	27/779 (3.47)	101/3293 (3.07)	1.130	0.566	0.744, 1.715
2001	27/861 (3.14)	126/3616 (3.48)	0.900	0.613	0.598, 1.355
2002	30/958 (3.13)	152/4038 (3.76)	0.832	0.347	0.566, 1.223
2003	32/1035 (3.09)	182/4328 (4.21)	0.735	0.100	0.508, 1.064
2004	35/1113 (3.14)	215/4562 (4.71)	0.667	0.022	0.470, 0.948
Ofloxacin					
1985	0/1 (0)	1/89 (1.12)	0.000	<0.001	4.071, 486.376
1986	15/102 (14.71)	2/102 (1.96)	7.500	<0.001	1.760, 31.963
1987	32/867 (3.69)	3/189 (1.59)	2.325	0.143	0.720, 7.514
1988	42/1243 (3.38)	9/332 (2.71)	1.246	0.541	0.613, 2.534
1989	46/1515 (3.04)	10/446 (2.24)	1.354	0.376	0.689, 2.661

Continued next page

Table I. Contd

Period ending	Proportion of ADRs that were anaphylaxis (%)		PRR		
year-end	individual fluoroquinolone (a/a + c)	all other fluoroquinolones (b/b + d)	point estimate	p-value	95% CI
1990	50/1676 (2.98)	13/565 (2.30)	1.297	0.402	0.710, 2.369
1991	52/1761 (2.95)	14/616 (2.27)	1.299	0.377	0.725, 2.327
1992	54/1803 (3.0)	16/707 (2.26)	1.323	0.316	0.763, 2.296
1993	55/1849 (2.97)	17/818 (2.08)	1.431	0.188	0.836, 2.450
1994	59/1908 (3.09)	18/867 (2.08)	1.489	0.131	0.884, 2.509
1995	60/1970 (3.05)	21/955 (2.20)	1.385	0.191	0.848, 2.263
1996	62/2029 (3.06)	22/1023 (2.15)	1.421	0.149	0.879, 2.298
1997	66/2121 (3.11)	27/1103 (2.45)	1.271	0.285	0.817, 1.977
1998	67/2181 (3.07)	39/1300 (3.0)	1.024	0.916	0.694, 1.511
1999	67/2217 (3.02)	53/1667 (3.18)	0.951	0.779	0.667, 1.355
2000	69/2244 (3.07)	76/2029 (3.75)	0.821	0.226	0.596, 1.131
2001	71/2264 (3.14)	99/2414 (4.10)	0.765	0.078	0.567, 1.032
2002	72/2288 (3.15)	127/2909 (4.37)	0.721	0.023	0.543, 0.957
2003	73/2301 (3.17)	158/3263 (4.84)	0.656	0.002	0.499, 0.860
2004	73/2314 (3.15)	194/3563 (5.44)	0.579	<0.001	0.445, 0.754

a Cumulative PRRs are for moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin and were calculated for the period from the market authorisation of the respective fluoroquinolone in Germany until 2004. Accordingly, for each fluoroquinolone the cumulative PRR for 2004 represents the total value over all years since its individual market authorisation. PPRs for fluoroquinolones with a cumulative total of ≤5 reports of anaphylaxis are not shown.

ADR = adverse drug reaction.

intake of the drug were considered to be at least possible. In addition, the reporting rate for anaphylaxis during the study period was highest for moxifloxacin (figure 3). Interestingly, the number of reports for any ADR associated with moxifloxacin that was received by the BfArM appeared to be roughly stable, or even to decrease, from 2000 to 2004, whereas the number of reports of anaphylaxis associated with moxifloxacin has steadily increased. Furthermore, the increase in the total number of cases of anaphylaxis associated with fluoroquinolones that has developed since 2000 seems to be mainly driven by reports associated with moxifloxacin (figures 5 and 6). Accordingly, the PRRs for moxifloxacin-associated anaphylaxis were significantly increased in the period 2001–2004 (table I).

There are several explanations for these findings, taking into consideration the limitations of the spontaneous reporting system. For instance, the awareness of drug safety and the willingness to submit spontaneous ADR reports is considered to have increased,[21] in particular over the last 20 years (the so-called secular trend), making it difficult to compare a drug that has already been marketed for a long time (e.g. ciprofloxacin from 1987; ofloxacin from 1985) and a drug more recently launched on the market (e.g. moxifloxacin from 1999; levofloxacin from 1998). We tried to address this point by calculating cumulative PRRs for fluoroquinolone-associated anaphylaxis for each of the four fluoroquinolones for every year since their marketing authorisation until 2004. Significantly increased PRRs for a period of 4 years were found in association with moxifloxacin. For ofloxacin, a single significantly increased PRR of 7.5 with a wide confidence interval was calculated in 1986. However, this PRR should be treated with caution since reporting of serious ADRs was first made compulsory for pharmaceutical companies in Germany in 1987 and, hence, it cannot be excluded that further cases of anaphylaxis occurred with other fluoroquinolones up until 1987, but were not reported. Non-significantly increased PRRs (≥2) were also calculated for moxifloxacin (in 1999), ofloxacin (1987), ciprofloxacin (1988) and levofloxacin (1998). Although increased PRRs for ofloxacin, ciprofloxacin and levofloxacin were noted, they were not significant, in contrast to those associated with moxifloxacin. In

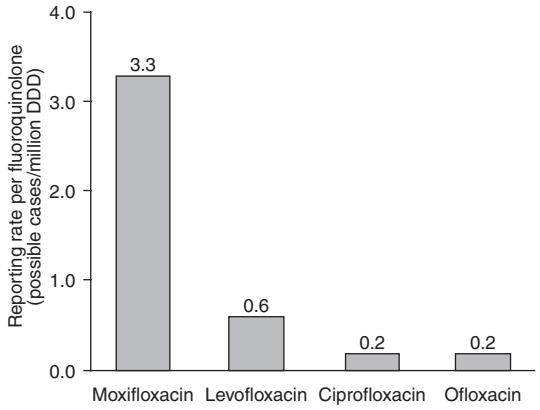

Fig. 3. Reporting rate for anaphylaxis associated with selected fluoroquinolones with a cumulative total of more than five reports in the period 1 January 1993–31 December 2004. The reporting rates were calculated as the total number of cases of anaphylaxis per individual fluoroquinolone received by the Federal Institute for Drugs and Medical Devices during this period that were considered to at least possibly have been correctly diagnosed as anaphylaxis and have a possible causal relationship with the incriminated fluoroquinolone divided by the estimated cumulative exposure for the respective fluoroquinolone in million defined daily doses (DDD) in the same period.

addition, consistently elevated PRRs over a longer period (≥3 years) were not seen with these fluoroquinolones

The higher reporting rate for moxifloxacin-associated anaphylaxis could also be due to the so-called Weber effect, suggesting that the ADR reporting rate for a new drug increases towards the end of the second calendar year of marketing and declines thereafter.[22] This effect may be seen with levofloxacin (figure 6), which gained marketing authorisation in Germany only 1 year before moxifloxacin and, hence, may be an appropriate comparator. However, the Weber effect does not exactly fit for moxifloxacin, which has the highest ADR reporting rate 4 years after marketing authorisation. In addition, the number of reports for levofloxacin-associated anaphylaxis decreases after the third year after marketing authorisation, whereas this continues to increase with moxifloxacin (figure 5). Levofloxacin has been associated with a higher number of spontaneous ADR reports concerning tendinopathies in some European countries,[4,23] including Germany, compared with other fluoroquinolones. This may be of importance with regard to the PRR for the spontaneous reports of levofloxacin-associated anaphylaxis, because the association between a drug and a reaction may be artificially decreased if another specific ADR is widely reported, as this dilutes the association by increasing the presence of the drug in ADR reports that are not associated with the reaction of interest.[7]

A disproportional reporting of moxifloxacin-associated cases of anaphylaxis could also occur if the company actively searches for such cases and, based on the reporting of single symptoms (e.g. hypotension, laryngeal oedema, urticaria), forms a deviating company diagnosis, i.e. anaphylaxis. To address this point we identified fluoroquinolone-associated cases of ADRs similar to anaphylaxis, i.e. circulatory and respiratory symptoms (excluding reports of anaphylaxis), but again the results were not substantially changed (figure 4).

With regard to the exposure data used in this study, it should be noted that these do not include prescription data from patients exempted from the compulsory health insurance in Germany, which accounts for approximately 10% of the German population.[20] However, the authors are not aware of any evidence suggesting different tendencies for the development of fluoroquinolone-associated ana-

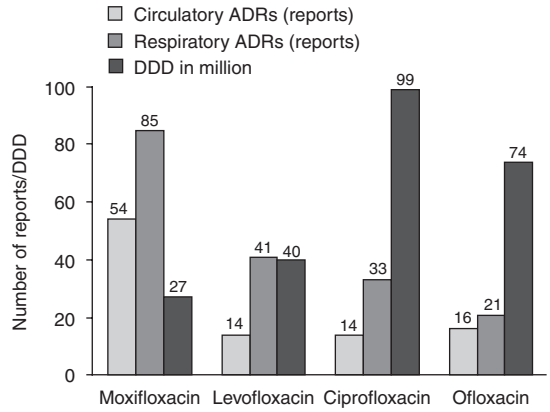

Fig. 4. Total number of reports of circulatory (circulatory failure, circulatory shock, shock) or respiratory (bronchospasm, aggravated bronchospasm, dyspnoea, laryngeal oedema, throat tightness) adverse drug reactions (ADRs), excluding those that reported the terms 'anaphylaxis', 'anaphylactic shock' and 'anaphylactic/anaphylactoid reaction', received by the Federal Institute for Drugs and Medical Devices for the period 1 January 1993–31 December 2004. The third bar shows the estimated cumulative exposure in the period under review. Only fluoroquinolones with a cumulative total exceeding ten cases are shown. **DDD** = defined daily doses.

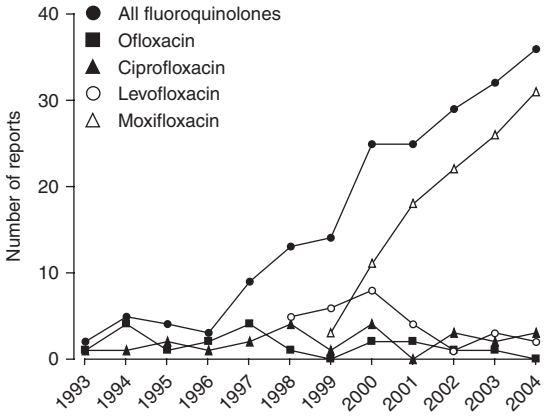

Fig. 5. Number of spontaneous reports per year that included the terms 'anaphylaxis', 'anaphylactic shock' and 'anaphylactic/anaphylactoid reaction' for selected fluoroquinolones received by the Federal Institute for Drugs and Medical Devices for the period 1 January 1993–31 December 2004, irrespective of their assessment with regard to the correctness of the diagnosis of anaphylaxis and the causal relationship with the drug. Only fluoroquinolones with a cumulative total of more than five reports are shown. The line indicating cases of anaphylaxis for all fluoroquinolones summarises all the reports of anaphylaxis received, not only for the four fluoroquinolones shown, but for all fluoroquinolones. The figure illustrates an increase in reported cases of moxifloxacin-associated anaphylaxis that seems to drive the increase in reports of anaphylaxis for all fluoroquinolones.

phylaxis in patients who are members of the compulsory health insurance compared with the 10% who are exempted.

A bias when connecting the data in ADR reports with the exposure to the drug could also occur if the exposure to moxifloxacin in the 10% of the German population who are exempted from the compulsory health insurance is considerably high. However, this bias could also apply to all other fluoroquinolones and would not affect the number of ADR reports itself.

The reporting rates per 1 million DDD found in this investigation were 3.3, 0.6, 0.2 and 0.2 for moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin, respectively (figure 3). Hence, there is a factor of 6–17 between the reporting rate for moxifloxacin and those for the other fluoroquinolones. Assuming that the reporting rates were in fact similar for the four fluoroquinolones (e.g. 0.6), this would either mean that the exposure to moxifloxacin was underestimated (by a factor of 6) or that the exposure with all the other three fluoroquinolones was accordingly overestimated. However, we feel that the mentioned uncertainties concerning the estimation of exposure are not likely to be of such a magnitude that they completely explain the observed differences in the reporting rates.

With regard to further bias, duplicate reporting should also be considered. Although routine measures are operating to detect duplicate reporting among spontaneous reports received by the BfArM, for instance by the inclusion of both the initial and follow-up reports, the possibility of duplicate reports cannot totally be excluded. However, duplicate reporting would probably occur at random and hence, would not be selective for one particular fluoroquinolone.

It should be noted that reporting rates calculated by applying the number of spontaneous ADR reports to estimates of exposure must be differentiated from calculations of ADR frequencies based on clinical studies. However, the total number of reports for a specific ADR may indicate the lower limit of its frequency. In addition, in the absence of data from clinical trials, it may be acceptable to compare the ADR profiles of drugs in the same

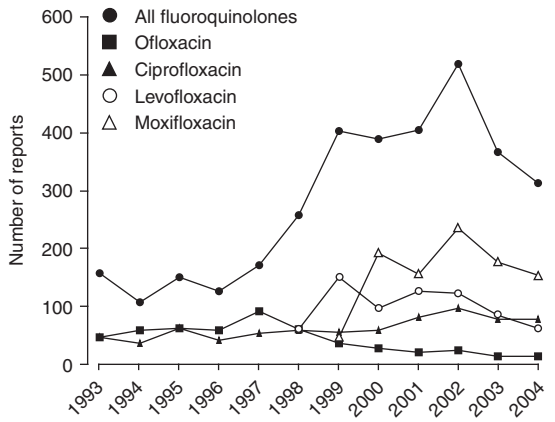

Fig. 6. Number of spontaneous reports of any adverse drug reaction (ADR) per year, including anaphylaxis, for selected fluoroquinolones received by the Federal Institute for Drugs and Medical Devices for the period 1 January 1993–31 December 2004, irrespective of the correctness of the diagnosis and the causal relationship with the drug. Only fluoroquinolones with a cumulative total of more than 500 ADRs are shown. The line indicating ADRs for all fluoroquinolones summarises reports received, not only for the four fluoroquinolones shown, but for all fluoroquinolones. The figure illustrates that the total of reported cases for any ADR appears to be roughly stable for the four fluoroquinolones since 2000.

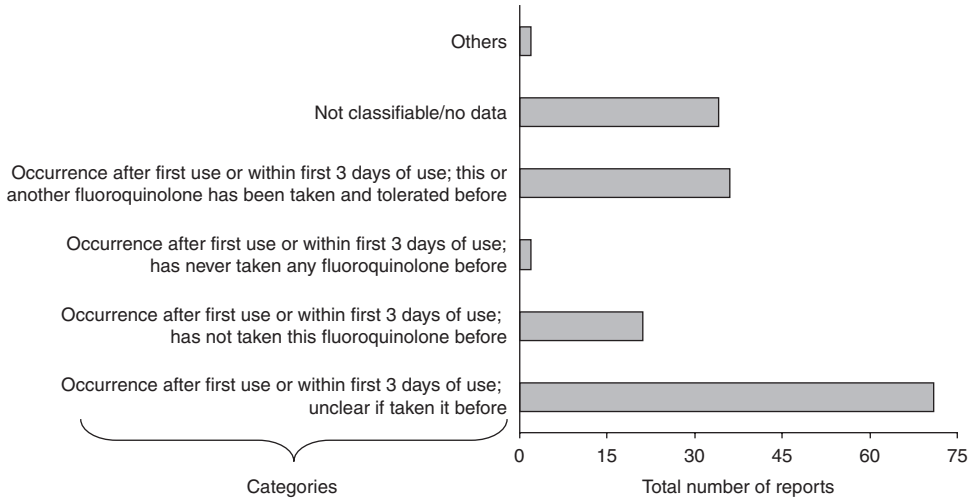

Fig. 7. Analysis of data concerning the time to onset of the adverse effect and history of previous fluoroquinolone intake provided with the 166 fluoroquinolone-associated cases of anaphylaxis reported to the Federal Institute for Drugs and Medical Devices in the period 1 January 1993– 31 December 2004 that have been assessed as at least possibly concerning the diagnosis anaphylaxis and possibly having a causal relationship with the drug.

therapeutic class based on data from spontaneous reports in conjunction with estimates of exposure. Many such studies have been published, including one study analysing fluoroquinolone-associated ADRs of any kind.[4] With regard to our study, it should be noted that, because of under-reporting, the true number of cases of fluoroquinolone-associated anaphylaxis that occurred in the period under review will likely be greater than the 166 cases identified.

It is difficult to assess these results from the spontaneous reporting system in Germany, which are also reflected in the WHO-database, as they indicate a higher reporting rate for anaphylaxis associated with moxifloxacin than with other fluoroquinolones and such a finding has not been described before, nor, to the best of our knowledge are there any published data on fluoroquinolone-associated anaphylaxis that are based on clinical or epidemiological studies. However, one reason for the lack of such data could be that, up until now, there has not been a signal that would justify initiating such studies. In a recent publication that provided an overview of the cumulative safety data on moxifloxacin, including data from postmarketing studies, anaphylaxis was not addressed.[24] There are numerous case reports informing about ciprofloxacin-induced anaphylaxis or anaphylactic reactions (in particular in patients with AIDS),[2] but only one anaphylactoid reaction[25] and one case of toxic epidermal necrolysis[26] associated with moxifloxacin have been described. In a recent study of 20 patients with hypersensitivity to antibacterials, moxifloxacin used as an alternative antibacterial was tolerated by 17 patients. One patient developed generalised urticaria after the first dose, one patient experienced nausea and one patient experienced tachycardia.[27] Hence, a publication bias appears unlikely with regard to moxifloxacin-associated anaphylaxis. Since the aforementioned publication investigating moxifloxacin as an alternative antibacterial in patients with antibiotic hypersensitivity was published in 2005, and the data lock point in the present investigation was December 2004, a channelling effect in our data based on this publication also appears unlikely. However, because of the lack of reports of moxifloxacin-associated anaphylaxis compared, for instance, with ciprofloxacin, moxifloxacin may have been considered safe in this regard by physicians and, hence, preferential prescribing of moxifloxacin to patients at risk for drug-associated anaphylaxis cannot be excluded. However, this assumption could also apply to levofloxacin.

It is within the scope of the spontaneous reporting system to identify differences in reporting rates for a

specific ADR within a class of drugs, which is a main result of this study. However, it is beyond the potential of the spontaneous reporting system to assess whether the differences in reporting rates reflect differences in occurrence rates. Hence, the question originating from the findings of the present investigation, whether individual representatives within the class of fluoroquinolones are associated with different risks for anaphylaxis, may only finally be elucidated in an appropriately designed epidemiological study, e.g. a case-control study.

Based on the assumption that with non-immune-mediated reactions no sensitisation phase is necessary, analysis of the affected individual's previous history of fluoroquinolone intake and time to the onset of the reaction suggests underlying non-immune-mediated mechanisms in a considerable number of cases (figure 7). It should be emphasised that, because of the nature of these data (ADR reports), this finding can only be considered an indirect suggestion and has no direct proof. However, this suggestion is endorsed by preclinical data describing the potency of fluoroquinolones for the induction of the release of vasoactive substances, such as histamine, from mast cells,[28] i.e. to induce non-immune-mediated, pseudo-allergic reactions, owing to the good intracellular penetration of the agents.[29,30] In addition, in a recent laboratory investigation, fluoroquinolone-specific IgE could only be detected, using an experimental approach, in 55% of patients with a history of immediate reactions to fluoroquinolones, suggesting underlying non-immune-mediated mechanisms in the other 45% of patients.[8]

From a pharmacovigilance point of view these data are of importance since physicians and patients should be aware that such reactions may already occur after first-ever intake of a fluoroquinolone. This may also be relevant for patients treated with a single injection, for instance, those with gonorrhoea.

It is well known that patients with concomitant viral infections in general, and patients with AIDS in particular, are more prone to develop hypersensitivity reactions to drugs.[3,6] Accordingly, several reports of hypersensitivity reactions to fluoroquinolones in HIV-infected patients have been described in the literature.[2,3] However, in our study, no cases of underlying HIV infection were reported.

Our finding that 55% of reports of fluoroquinolone–associated anaphylaxis were in females is in accordance with studies on the sex distribution of ADRs[4,6] and drug-induced anaphylaxis in particular.[7] The observation that the majority of reports were in individuals aged 20–49 years probably mirrors the higher exposure rate in these age groups.

In contrast to a recent investigation of drug-induced anaphylaxis in spontaneous ADR reports,[7] in our investigation the drug was administered intravenously in only 3% of reports of anaphylaxis. This may be of importance, since intravenous drug application usually takes place under a physician's surveillance, whereas oral administration is typical for treatment in everyday life and, hence, in the case of anaphylaxis, immediate care may not be available, unlike with hospital administration. Nevertheless, in our study only 2% of the reports were associated with a fatal outcome.

Conclusion

In summary, considering all data available, anaphylaxis may occur with various fluoroquinolones. In addition, the data presented provide a signal that drug-associated anaphylaxis could occur more often with moxifloxacin than with other fluoroquinolones. Appropriate epidemiological studies could help to refute or validate this signal. In addition, patients and physicians should be aware that, due to non-immune-mediated effects, fluoroquinolone-associated anaphylaxis may occur after first-ever intake.

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