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Incidence of Allergic Reactions Associated with Antibacterial Use in a Large, Managed Care Organisation

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Abstract

Background: Data on the incidence of serious allergic reactions to fluoroquinolone antibacterials are mainly derived from spontaneous reports that cannot be used to accurately estimate incidence.

Methods: This study estimated the drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin and phenoxymethylpenicillin potassium exposure, using claims for healthcare services with confirmation through medical record abstraction within a large health insurer database. Cohorts exposed to each antibacterial of interest (moxifloxacin, levofloxacin, ciprofloxacin, gatifloxacin, cephalosporins and penicillin) were identified, and followed for 14 days for anaphylaxis (9th revision of the *International Classification of Diseases* [ICD-9] code 995.0), other allergic drug reactions (ICD-9 995.2, 995.3) or cardiopulmonary resuscitation.

Results: The incidence per 10 000 first dispensings of any allergic diagnosis made in the hospital or emergency department was similar for moxifloxacin (4.3; 95% CI 3.5, 5.3), penicillin (4.7; 95% CI 3.8, 5.7) and ciprofloxacin (5.4; 95% CI 4.4, 6.5). The incidence for moxifloxacin was lower than that for levofloxacin (8.7; 95% CI 7.4, 10.0), gatifloxacin (6.7; 95% CI 5.6, 7.9) and the cephalosporins (7.5; 95% CI 6.3, 8.8). The incidence of anaphylaxis/anaphylactoid reactions after first dispensings was similar for the fluoroquinolones: 0.1 (95% CI 0.0, 0.3) for ciprofloxacin, 0.3 (95% CI 0.1, 0.5) for moxifloxacin, 0.3 (95% CI 0.1, 0.6) for gatifloxacin and 0.5 (95% CI 0.3, 0.9) for levofloxacin; and comparable with that of the cephalosporins (0.2; 95% CI 0.0, 0.4) and penicillin (0.1; 95% CI 0.0, 0.3).

Conclusions: Anaphylactic reactions were rare and their incidence did not differ substantially among the drug groups studied. By determining the occurrence of reactions following defined exposures, these results provide a context for the interpretation of spontaneous reports of allergic reactions.

Background

Fluoroquinolones are broad-spectrum antibacterials, used primarily for the treatment of respiratory tract infections, sexually transmitted diseases, skin and soft-tissue infections and urinary tract infections.[1] As a class, fluoroquinolones are generally considered safe and effective, with the most common adverse events being mild and self-limiting, such as gastrointestinal effects, skin rashes, dizziness and headache.[1,2] However, serious adverse effects have been reported in the postmarketing phase, such as cardiac arrhythmia, hepatic toxicity, haemolytic uraemic syndrome, tendon disorders and anaphylaxis, which in some instances have resulted in labelling changes, restriction of use and removal of several products from the market.[2]

Reports of anaphylactoid and anaphylactic reactions to fluoroquinolones are rare, and have mainly occurred in the postmarketing rather than in clinical trial or premarketing experience.[3] Both anaphylactic and anaphylactoid reactions lead to the activation of mast cells and the release of mediators including histamine. Anaphylaxis is mediated by IgE and is an acute, life-threatening, systemic reaction occurring after exposure to a sensitising antigen in a previously sensitised individual.[4-6] Symptoms usually occur within seconds to minutes after exposure, and the usual clinical presentation is respiratory distress and vascular collapse.[5,6] Treatment is typically with adrenaline (epinephrine) injection or intravenous infusion, and cardiovascular and respiratory support with resuscitation if cardiac arrest occurs.[5] Anaphylactoid reactions are clinically similar to anaphylactic reactions, but may occur after first exposure to a drug and are not mediated by IgE.[4,7,8] The two terms are often used interchangeably, and the diagnosis code of 995.0 under the 9th revision of the *International Classification of Diseases* (ICD-9) does not distinguish between anaphylactic and anaphylactoid reactions.

The epidemiology of anaphylaxis is not well described, and estimates of incidence vary due to differences in populations studied, differences in case definitions and possible under-reporting.[6,9,10] Food, drugs and insect venom are the most common causes of anaphylactic reactions. Published information on the occurrence of serious allergic reactions to fluoroquinolones is limited and based on spontaneous reports with anaphylactic reactions to fluoroquinolones estimated at 0.5–1.2 cases per 100 000 patients.[11] A literature review noted that anaphylactic reactions occurring within 1 hour from quinolone ingestion have been reported in 167 individuals, with 39 cases of anaphylactic shock.[3] Estimating incidence based on spontaneous reporting is problematic because under-reporting of cases is likely, and the size of the exposed population from which the cases arose is difficult to determine. Spontaneous reports of anaphylactoid and anaphylactic reactions after the use of fluoroquinolones are documented with some suggestion that they are more common with moxifloxacin.[8,12,13] Based on spontaneous adverse event reporting to the US FDA, the incidence of anaphylactoid reactions in the US after ciprofloxacin exposure has been estimated at 1.2 per 100 000 prescriptions.[14] Allergic cross-reactivity may exist between older and newer quinolones because of their similar chemical structure, and it is recommended to avoid treatment with another fluoroquinolone when a severe hypersensitivity reaction has occurred with one.[7,14,15] There are reports of anaphylactoid reactions to certain fluoroquinolones without the presence of drug-specific IgE or evidence of cross-reactivity to other quinolones.[7,8,15] One published case report describes an anaphylactoid reaction following the use of levofloxacin,[7] and one following moxifloxacin exposure.[15] Other fluoroquinolones for which anaphylactoid reactions have been documented are nalidixic acid, pipemidic acid, pefloxacin, ofloxacin and norfloxacin.[8]

To provide a context for postmarketing reports of fluoroquinolone-induced anaphylactic reactions, we conducted a systematic study of the incidence of serious allergic reactions, including anaphylaxis/anaphylactoid reactions, in a population defined by antibacterial dispensings within a specified time range to derive cases from a known underlying population of exposed patients.

Methods

This was a cohort study of antibacterial users conducted in a large US health insurance claims database, the Ingenix Research Data Mart. During the study timeframe (1 July 2000–30 June 2004), this research database included complete health services utilisation information (claims for all outpatient pharmacy dispensations, inpatient and outpatient services, and procedures, including the associated diagnoses and costs) for approximately 10 million patients. Geographical representation of the insured population in the research database is concentrated in the Midwest and Southeast, and members have a similar age distribution as the US population for all age categories through 64 years.

This study followed Health Insurance Portability and Accountability Act guidelines for the protection of patient confidentiality. Since this study used protected health information to link insurance claims to patient medical records, we operated with the oversight of an Institutional Review Board (IRB) who approved our protocol and privacy practices, and we obtained a waiver of authorisation from a Privacy Board to allow the use of protected health information without obtaining patient authorisation. The health information of study subjects was used for this study in accordance with the approved study protocol and privacy practices.

The study population comprised patients receiving at least one dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethylpenicillin potassium or a combined group of first-, second- and third-generation cephalosporins. Patients who were dispensed more than one study drug were placed into each relevant drug group and thus could appear in more than one treatment group. We determined the number of unique individuals with a first dispensing of moxifloxacin, and selected a random sample of individuals in each of the other five drug groups approximately equal in size to the moxifloxacin group. We formed two sets of study drug groups for separate analyses, one limited to first dispensings of the antibacterial within the study timeframe and one including all dispensings for each patient within the study timeframe.

An index date was identified for each member in each of the drug groups that represented each dispensing of a study drug throughout the study timeframe. The baseline period was the 183 days before the index date; for persons with multiple index dates, baseline characteristics were determined in the 183 days before each dispensing. Age group, sex, geographical region and medical conditions that might be indications for the study antibacterials, identified by ICD-9 codes associated with outpatient or inpatient physician services, were determined from enrolment and claims for services.

We followed each person for 14 days after each study drug dispensing and counted the first emergency department (ED) or hospitalisation (inpatient) visit during this time. A serious allergic reaction was defined as the presence of at least one claim for services occurring during one of these inpatient or ED visits bearing ICD-9 diagnosis codes of 995.0 (anaphylactic shock), 995.2 (unspecified adverse effect of drug), 995.3 (allergy, unspecified), a current procedural terminology (CPT) code of 92950 for cardiopulmonary resuscitation or a healthcare common procedure coding system (HCPCS) code for adrenaline injection (J7640). We defined four separate categories of serious allergic reactions: anaphylactic (ICD-9 995.0; note that the ICD-9 code does not distinguish between anaphylactic or anaphylactoid reactions), resuscitation (CPT 92950 or HCPCS J7640), drug allergy (ICD-9 995.2) and allergy (ICD-9 995.3). If more than one event occurred during the visit, only one was counted based on severity in the order listed above. We also included a grouped category of any allergic event that contained all four types of events. Events were ascertained after the first eligible dispensing of each drug and after all dispensings, and results presented separately.

For each of the 84 possible cases (from 77 patients), we sought medical records for confirmation of anaphylaxis. We used an abstraction form to record information in a standardised format from the medical record that might verify the occurrence of

an anaphylactoid or anaphylactic reaction. All completed abstraction forms and supporting documentation were reviewed by a clinician (ED physician) for determination of case status, date of onset and any exposure noted as presumed to precipitate the event. The clinical reviewer classified possible cases as definite anaphylaxis or not based on available documentation and not blinded to suspected drug exposures.

Frequency distributions of dispensings for each drug group were stratified by demographic variables and baseline medical claims. The incidence of serious allergic outcomes according to each drug group and by first eligible and all dispensings were calculated as the number of events divided by the total number of dispensings and expressed per 10 000 dispensings with 95% CI.[16]

Results

A total of 201 198 initiators of moxifloxacin were identified along with 197 659 levofloxacin initiators, 188 868 gatifloxacin initiators, 197 952 ciprofloxacin initiators, 193 939 cephalosporin initiators and 199 862 penicillin initiators. The moxifloxacin initiators averaged 1.3 dispensings each, whereas levofloxacin initiators averaged 1.5 each, gatifloxacin initiators 1.3, ciprofloxacin initiators 1.4, cephalosporin initiators 1.5 and penicillin initiators 1.3. Most patients in each drug group had only a single dispensing of that drug (83% moxifloxacin, 73% levofloxacin, 82% gatifloxacin, 77% ciprofloxacin, 69% cephalosporin and 82% penicillin).

Baseline characteristics before all eligible dispensings of the study drugs are shown in table I. The age distribution for cephalosporin and penicillin users was somewhat younger than that of fluoroquinolone users, and the proportion of females to males was higher for fluoroquinolone than for cephalosporin or penicillin users. In general, claims for upper respiratory tract infections were more likely to precede the dispensing of a cephalosporin than a fluoroquinolone. Claims for lower respiratory tract infections were more likely to take place prior to a dispensing of levofloxacin and gatifloxacin than before a dispensing of the other study drugs. Less than 2% of patients in each drug group had claims for any of the serious allergic reactions that represented study outcome events in the baseline period.

Table II displays the incidence per 10 000 dispensings of each type of outcome event by study drug group following first or all dispensings. The incidence of anaphylaxis following first eligible dispensings was low for all antibacterial groups, and varied from a high in the levofloxacin group of 0.5 to a low of 0.1 in the ciprofloxacin and penicillin groups. The 95% CI for the incidence estimates overlapped for all drug groups, but the point estimate of levofloxacin was higher than the upper limit of the 95% CI for ciprofloxacin, cephalosporin and penicillin. The incidence of anaphylaxis after first eligible dispensings was similar for the moxifloxacin (0.3; 95% CI 0.1, 0.5), cephalosporin (0.2; 95% CI 0.1, 0.4) and gatifloxacin (0.3; 95% CI 0.1, 0.6) groups (table II). The incidence of cardiopulmonary resuscitation after first eligible dispensings was highest for levofloxacin (0.6; 95% CI 0.3, 0.10) and lowest for moxifloxacin (0.1; 95% CI 0.0, 0.2), and the 95% CI for these two groups did not overlap. The incidence of resuscitation after all dispensings was lowest for the penicillin group. A separate analysis of study outcomes standardised by a baseline diagnosis of asthma or a baseline diagnosis of a study outcome did not differ materially from these results (data not shown).

The incidence of 'adverse effect of drug' (ICD-9 995.2) reactions following first eligible dispensings was higher for levofloxacin (4.2; 95% CI 3.4, 5.2) than for moxifloxacin (2.0; 95% CI 1.5, 2.7), ciprofloxacin (2.5; 95% CI 1.9,3.2), cephalosporin (2.4; 95% CI 1.8, 3.2) or penicillin (2.1; 95% CI 1.5, 2.8) [table II]. Unspecified allergic reactions after first and all dispensings were highest for the cephalosporin and lowest for the moxifloxacin group. The incidence of any allergic reaction (all events combined) after first eligible dispensings was lowest for moxifloxacin, which was comparable to the penicillin group. After all dispensings, the incidence of any reaction for the penicillin group was slightly lower than that for the moxifloxacin group.

Table I. All eligible antibacterial dispensings from 1 July 2000 through 30 June 2004 by baseline[a] characteristics

Characteristics	Moxifloxacin (n = 252 579)		Levofloxacin (n = 290 365)		Gatifloxacin (n = 238 526)		Ciprofloxacin (n = 272 256)		Cephalosporins (n = 295 548)		Penicillin (n = 250 598)	
	n	%	n	%	n	%	n	%	n	%	n	%
Demographics												
Age group (years)												
0–9	13 965	5.5	596	0.2	324	0.1	26 697	9.8	67 851	23.0	14 160	5.7
10–19	7 585	3.0	6 103	2.1	5 059	2.1	17 816	6.5	39 559	13.4	34 484	13.8
20–29	21 476	8.5	26 670	9.2	22 511	9.4	28 885	10.6	28 122	9.5	37 877	15.1
30–39	52 466	20.8	59 188	20.4	53 017	22.2	50 453	18.5	47 511	16.1	49 756	19.9
40–49	67 773	26.8	78 834	27.1	67 220	28.2	61 760	22.7	51 542	17.4	56 118	22.4
50–59	56 452	22.4	71 601	24.7	56 272	23.6	53 156	19.5	39 929	13.5	40 828	16.3
60–64	17 711	7.0	24 934	8.6	18 140	7.6	17 840	6.6	11 585	3.9	10 651	4.3
65+	15 151	6.0	22 439	7.7	15 983	6.7	15 649	5.7	9 449	3.2	6 724	2.7
Sex												
male	104 495	41.4	120 660	41.6	94 917	39.8	109 752	40.3	132 633	44.9	117 108	46.7
female	148 084	58.6	169 705	58.4	143 609	60.2	162 504	59.7	162 915	55.1	133 490	53.3
Baseline medical claims[b]												
Genitourinary infections												
cystitis	1 349	0.5	2 910	1.0	2 547	1.1	7 360	2.7	2 887	1.0	1 633	0.7
urinary tract infections	7 783	3.1	15 714	5.4	14 498	6.1	35 889	13.2	16 099	5.4	9 025	3.6
prostatitis	951	0.4	2 326	0.8	1 166	0.5	7 682	2.8	1 271	0.4	943	0.4
Respiratory infections												
streptococcal pharyngitis	1 266	0.5	1 430	0.5	9 408	3.9	3 687	1.4	10 557	3.6	4 976	2.0
acute sinusitis	24 113	9.5	44 499	15.3	38 826	16.3	27 220	10.0	44 687	15.1	15 802	6.3
acute pharyngitis	10 603	4.2	16 657	5.7	34 331	14.4	19 985	7.3	38 815	13.1	20 900	8.3
acute tonsillitis	1 183	0.5	1 698	0.6	6 298	2.6	2 838	1.0	7 277	2.5	3 221	1.3
acute laryngitis/tracheitis	1 247	0.5	1 787	0.6	4 703	2.0	2 576	0.9	5 483	1.9	1 024	0.4
acute upper respiratory	13 098	5.2	22 126	7.6	43 803	18.4	26 249	9.6	50 088	16.9	16 381	6.5
otitis	10 421	4.1	16 640	5.7	51 168	21.5	33 978	12.5	59 404	20.1	12 994	5.2
acute bronchitis	15 167	6.0	27 624	9.5	21 773	9.1	17 008	6.2	24 918	8.4	10 256	4.1
pneumonia	6 312	2.5	9 974	3.4	6 012	2.5	4 421	1.6	6 940	2.3	2 264	0.9
Skin/soft tissue infection	4 090	1.6	7 083	2.4	13 817	5.8	10 368	3.8	15 620	5.3	4 476	1.8

a Baseline = 183 days before any dispensing.

b Claims for medical conditions occurring in the 183 days before drug dispensings (not including the day of dispensing).

Table II. Incidence of emergency department visit or hospitalisation with claims for a serious allergic reaction after first and all dispensings

Drug group and outcome event	First dispensings			All dispensings		
	dispensings (n)	events (n)	incidence (95% CI)[a]	dispensings (n)	events (n)	incidence (95% CI)[a]
Moxifloxacin						
Anaphylaxis	201 198	5	0.3 (0.1, 0.5)	252 579	8	0.3 (0.2, 0.6)
Resuscitation	201 198	1	0.1 (0.0, 0.2)	252 579	4	0.2 (0.1, 0.4)
Adverse effect of drug	201 198	41	2.0 (1.5, 2.7)	252 579	55	2.2 (1.7, 2.8)
Allergy	201 198	40	2.0 (1.4, 2.7)	252 579	54	2.1 (1.6, 2.8)
Any allergic reaction[b]	201 198	87	4.3 (3.5, 5.3)	252 579	121	4.8 (4.0, 5.7)
Levofloxacin						
Anaphylaxis	197 659	10	0.5 (0.3, 0.9)	290 365	10	0.3 (0.2, 0.6)
Resuscitation	197 659	12	0.6 (0.3, 1.0)	290 365	20	0.7 (0.4, 1.0)
Adverse effect of drug	197 659	83	4.2 (3.4, 5.2)	290 365	102	3.5 (2.9, 4.3)
Allergy	197 659	66	3.3 (2.6, 4.2)	290 365	84	2.9 (2.3, 3.6)
Any allergic reaction[b]	197 659	171	8.7 (7.4, 10.0)	290 365	216	7.4 (6.5, 8.5)
Gatifloxacin						
Anaphylaxis	188 868	5	0.3 (0.1, 0.6)	238 526	5	0.2 (0.1, 0.5)
Resuscitation	188 868	6	0.3 (0.1, 0.7)	238 526	8	0.3 (0.2, 0.6)
Adverse effect of drug	188 868	55	2.9 (2.2, 3.8)	238 526	66	2.8 (2.2, 3.5)
Allergy	188 868	60	3.2 (2.5, 4.1)	238 526	86	3.6 (2.9, 4.4)
Any allergic reaction[b]	188 868	126	6.7 (5.6, 7.9)	238 526	165	6.9 (5.9, 8.0)
Ciprofloxacin						
Anaphylaxis	197 952	2	0.1 (0.0, 0.3)	272 256	3	0.1 (0.0, 0.3)
Resuscitation	197 952	3	0.2 (0.0, 0.4)	272 256	7	0.3 (0.1, 0.5)
Adverse effect of drug	197 952	49	2.5 (1.9, 3.2)	272 256	71	2.6 (2.1, 3.3)
Allergy	197 952	52	2.6 (2.0, 3.4)	272 256	72	2.6 (2.1, 3.3)
Any allergic reaction[b]	197 952	106	5.4 (4.4, 6.5)	272 256	153	5.6 (4.8, 6.6)
Cephalosporins						
Anaphylaxis	193 939	3	0.2 (0.0, 0.4)	295 548	6	0.2 (0.1, 0.4)
Resuscitation	193 939	6	0.3 (0.1, 0.6)	295 548	8	0.3 (0.1, 0.5)
Adverse effect of drug	193 939	47	2.4 (1.8, 3.2)	295 548	67	2.3 (1.8, 2.9)
Allergy	193 939	89	4.6 (3.7, 5.6)	295 548	129	4.4 (3.7, 5.2)
Any allergic reaction[b]	193 939	145	7.5 (6.3, 8.8)	295 548	210	7.1 (6.2, 8.1)
Penicillin						
Anaphylaxis	199 862	2	0.1 (0.0, 0.3)	250 598	2	0.1 (0.0, 0.3)
Resuscitation	199 862	3	0.2 (0.0, 0.4)	250 598	3	0.1 (0.0, 0.3)
Adverse effect of drug	199 862	41	2.1 (1.5, 2.8)	250 598	53	2.1 (1.6, 2.7)
Allergy	199 862	47	2.4 (1.8, 3.1)	250 598	56	2.2 (1.7, 2.9)
Any allergic reaction[b]	199 862	93	4.7 (3.8, 5.7)	250 598	114	4.6 (3.8, 5.4)

a Incidence (number of events/number of dispensings) per 10 000 dispensings.

b Anaphylaxis + resuscitation + adverse effect of drug + allergy, unspecified.

We obtained medical records for 64 of 77 (83.1%) patients for whom we sought them, and confirmed anaphylaxis in 1 of 35 (2.9%) patients on the basis of a claim for resuscitation, while 16 of 28 (57.1%) patients with a code for anaphylaxis were confirmed by clinical review to have anaphylaxis. The incidence of confirmed anaphylaxis was lower than the claims-based incidence, and cases where anaphylaxis was attributed to the claims-based exposure was only a fraction of the total (table III). The

incidence of confirmed anaphylaxis is quite similar when broken down according to occurrence following all dispensings, first dispensings or repeat dispensings: a pattern that does not suggest sensitisation from prior exposure (table IV).

Discussion

This study provides population-based estimates of the incidence of serious allergic reactions after exposure to four fluoroquinolones, cephalosporins and phenoxymethylpenicillin potassium in a managed care setting. These reflect the incidence of allergic reactions occurring in an ED or inpatient setting within 2 weeks after outpatient dispensing of the drugs. Estimates were provided both for exposure after first eligible dispensings only and after all dispensings (more than one per person) within the study time period. The incidence of any serious allergic reaction, including anaphylaxis, cardiopulmonary resuscitation, adverse effect of drug and unspecified allergy, was low and varied somewhat by drug, with the lowest (about 4 cases per 10 000 dispensings) found after first eligible dispensings of moxifloxacin and all dispensings of penicillin. The incidence of anaphylaxis was lowest for ciprofloxacin and penicillin users (1 per 100 000 first eligible dispensings). This incidence is similar to the only currently published estimate of anaphylaxis in ciprofloxacin users of 1.2 per 100 000 prescriptions in the US.[14]

The incidence of anaphylactic reactions after penicillin exposure has been reported at one to five per 10 000 patient treatments,[6] about 10-fold higher than that found in the current study. However, when we include all serious allergic reactions to penicillin, the incidence was 4.6 per 10 000 dispensings. There are several possible explanations for the relatively low incidence of penicillin anaphylaxis found. First, most prior estimates were based

Table III. Incidence of claim-identified and chart-verified cases of anaphylaxis occurring in the 14 days after all dispensings[a]

Drug group and verification	Dispensings (n)	Events (n)	Incidence (95% CI)[b]
Moxifloxacin			
Claims-defined	252 579	8	0.3 (0.2, 0.6)
Chart-verified	252 579	4	0.2 (0.1, 0.4)
Attributed to moxifloxacin[c]	252 579	3	0.1 (0.0, 0.3)
Levofloxacin			
Claims-defined	290 365	10	0.3 (0.2, 0.6)
Chart-verified	290 365	6	0.2 (0.1, 0.4)
Attributed to levofloxacin[c]	290 365	4	0.1 (0.0, 0.3)
Gatifloxacin			
Claims-defined	238 526	6	0.2 (0.1, 0.5)
Chart-verified	238 526	1	0.0 (0.0, 0.2)
Attributed to gatifloxacin[c]	238 526	0	0.0 (0.0, 0.1)
Ciprofloxacin			
Claims-defined	272 256	3	0.1 (0.0, 0.3)
Chart-verified	272 256	2	0.1 (0.0, 0.2)
Attributed to ciprofloxacin[c]	272 256	0	0.0 (0.0, 0.1)
Cephalosporins			
Claims-defined	295 548	8	0.3 (0.1, 0.5)
Chart-verified	295 548	3	0.1 (0.0, 0.3)
Attributed to cephalosporin[c]	295 548	2	0.1 (0.0, 0.2)

a Met claims definition for anaphylaxis (ICD-9 code 995.0).

b Incidence (number of events/number of dispensings) per 10 000 dispensings.

c Precipitating exposure documented by health professional in medical record.

ICD-9 = 9th revision of the *International Classification of Diseases*.

Table IV. Comparison of incidence of chart-verified anaphylactic events after first, all and repeat dispensings

Drug group and dispensing type	Dispensings (n)	Events (n)	Incidence (95% CI)[a]
Moxifloxacin			
First	201 196	4	0.2 (0.1, 0.5)
All	252 576	4	0.2 (0.1, 0.4)
Repeat	51 380	0	0.0 (0.0, 0.5)
Levofloxacin			
First	197 658	6	0.3 (0.1, 0.6)
All	290 364	6	0.2 (0.1, 0.4)
Repeat	92 706	0	0.0 (0.0, 0.3)
Gatifloxacin			
First	188 867	1	0.1 (0.0, 0.3)
All	238 525	1	0.0 (0.0, 0.2)
Repeat	49 658	0	0.0 (0.0, 0.5)
Ciprofloxacin			
First	197 952	1	0.1 (0.0, 0.2)
All	272 256	2	0.1 (0.0, 0.2)
Repeat	74 304	1	0.1 (0.0, 0.6)
Cephalosporins			
First	193 939	2	0.1 (0.0, 0.3)
All	295 548	2	0.1 (0.0, 0.2)
Repeat	101 609	0	0.0 (0.0, 0.2)

a Incidence (number of events/number of dispensings) per 10 000 dispensings.

on parenteral penicillin and we studied oral penicillin.[17] Secondly, many individuals with known penicillin allergies would not have been re-exposed (even those listed as first exposures in our data may have previously taken penicillin without an allergic reaction); this would mean that our exposure cohort was preselected to have a lower likelihood of anaphylaxis. Thirdly, some anaphylactic episodes may have been mislabelled as 'allergic events'. Lastly, episodes (fatal and non-fatal) not reaching the hospital were not included in our numerator resulting in an underestimate of incidence.

Several strengths of this study were noteworthy, including the large sample size (approximately 200 000 first eligible dispensings of each study drug), the ability to establish temporal sequence of drug dispensing and event onset and the systematic way in which events were identified in a defined study population that is representative of insured patients in the US. Unlike estimates based on spontaneous reports, the denominator used in this study accurately reflects the population from which the cases arose and there is a relatively complete collection of cases.

Some study limitations should be noted in interpreting the results. The definition of serious allergic reaction is based on diagnoses from billing claims without medical record confirmation. Thus, diagnosis codes appearing on claims before a definitive diagnosis is established might be captured, resulting in overestimation of events. The rarity of the events identified here would indicate that use of a claims definition did not greatly overestimate the incidence. In addition, events in this study are defined as the occurrence of claims in a hospital or ED setting in the 14 days after a study drug dispensing, and we could not definitively attribute the event to an exposure to one of the study drugs. Other possible causes, such as foods, insect venom, other drugs administered in the same timeframe or other allergens, cannot be ruled out. Serious events resulting in death outside of the hospital that did not generate billing claims for emergency, medical or hospital services would not be captured in the database. However, all claims for cardiopulmonary resuscitation, fatal or not, that occurred in an ED or inpatient setting in the 14 days after study drug dispensings were captured. Underestimation of anaphylaxis is possible if a true anaphylactic event were coded as an unspecified allergic reaction or adverse drug effect instead of anaphylaxis. In a community ED study in Minnesota, of the 17 cases of anaphylaxis identified in a 4-month period, 13 were diagnosed as 'allergic reactions' (ICD-9 code of 995.3).[9] We examined this code as a separate outcome and found, as with the anaphylaxis outcome, that the highest incidence after first eligible dispensings was with levofloxacin, with comparable incidences in the other antibacterial groups. As with all studies using administrative claims data, exposure is measured by the documentation of a dispensing; information on the actual timing and amount of drug used is not available.

Conclusions

The results of this study provide a context for interpretation of spontaneous reports of serious allergic reactions following fluoroquinolone exposure. The incidence of anaphylaxis is fairly comparable across the fluoroquinolone groups and not significantly different to that of cephalosporins or penicillin. In addition, the incidence of anaphylaxis following repeat dispensings did not differ significantly among the drug groups.

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