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Adverse Drug Reactions Related to the Use of Fluoroquinolone Antimicrobials

An Analysis of Spontaneous Reports and Fluoroquinolone Consumption Data from Three Italian Regions

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Abstract

Objective: To analyse and compare with one another and with other antibacterial drugs the adverse drug reactions (ADRs) of the different fluoroquinolones currently used in Italy, spontaneously reported from doctors in three northern Italian regions.

Methods: The data on fluoroquinolones and other antibacterials were obtained from the spontaneous reporting system database of Emilia Romagna, Lombardy and the Veneto, which are the principal contributors to the Italian spontaneous surveillance system. The fluoroquinolone ADRs with a causality assessment of certain, probable or possible (according to WHO criteria), reported between January 1999 and December 2001, were selected and toxicity profiles of individual drugs were described and compared with one another. The reports were also correlated with sex and age of patients and with regional prescription data to estimate individual fluoroquinolone reporting rate of adverse events.

Results: During the study period, 10 011 reports were received by the system (a mean annual reporting rate of approximately 185 per million inhabitants): 1920 referred to systemic antimicrobials, of which 432 (22.5%) involved fluoroquinolones.

Pefloxacin was associated with the highest reporting rate (982 reports/daily defined dose/1000 inhabitants/day), followed by moxifloxacin (356), rufloxacin (221) and lomefloxacin (196). The most frequently reported reactions to fluoroquinolones involved the skin, but their percentage (25%) was significantly lower ($p < 0.01$) than those of other systemic antimicrobials (58.5%), whereas the percentages of reactions involving the central nervous (12.2 vs 3.6%), musculoskeletal (14.7 vs 0.3%) and psychiatric systems (9.3 vs 1.8%) were signifi-

cantly higher ($p < 0.01$). We found some significant differences in the safety profiles of individual fluoroquinolones: ciprofloxacin was more frequently associated with skin reactions ($p < 0.01$), levofloxacin and pefloxacin with musculoskeletal ($p < 0.01$), and rufloxacin with psychiatric disorders ($p < 0.05$). Levofloxacin was the fluoroquinolone associated with the highest rate of serious tendon disorders; phototoxic reactions were more frequent with lomefloxacin, and toxic epidermal necrolysis and Stevens-Johnson syndrome were seen only with ciprofloxacin.

Conclusions: The differences in the safety profiles should be taken into account when prescribing a fluoroquinolone to individual patients.

Fluoroquinolone antimicrobials are used to treat various infections, and the newer drugs in this class have a broader spectrum of activity that better covers Gram-positive bacteria and even anaerobes.

On the basis of spectrum of activity, several classifications have been proposed, distinguishing three or four generations of fluoroquinolones.[1-7] First-generation fluoroquinolones (e.g. nalidixic acid) are moderately active against Gram-negative bacteria and used to treat urinary tract infections; second-generation fluoroquinolones (e.g. norfloxacin, lomefloxacin and ciprofloxacin) have broader Gram-negative activity that also includes *Pseudomonas* and are also partially active against Gram-positive organisms (*Staphylococcus aureus* but not *Streptococcus pneumoniae*). Some authors classify in a IIb-generation group agents with improved Gram-positive activity such as sparfloxacin and grepafloxacin.[3,5] Third-generation fluoroquinolones have expanded activity against *S. pneumoniae* and the common atypical organisms (e.g. levofloxacin); the fourth generation includes agents with significant anaerobic coverage (e.g. moxifloxacin and trovafloxacin, a fluoronaphthyridone related to the fluoroquinolone antibacterials). In some classifications, levofloxacin is considered a second-generation[5,7] and moxifloxacin a third-generation fluoroquinolone.[1-3,5]

Adverse effects are the 'Achilles heel' of this class of antimicrobials: a number of molecules have been withdrawn from the market or their development discontinued because of serious adverse reactions. Fleroxacin was withdrawn in 1990 because of phototoxicity[8] and temafloxacin in 1992 (shortly after its registration) because of 95 cases of severe hypoglycaemia, hepatic and renal dysfunction, haemolytic anaemia and anaphylaxis (the so-called temafloxacin syndrome), some of which were fatal.[9] It is interesting to note that trials involving more than 3000 patients before its registration indicated that temafloxacin was at least as well tolerated as other fluoroquinolones and had a low incidence of known class effects such as phototoxicity.[10] The development of several fluoroquinolones, such as clinafloxacin, Bay 3118 and tosufloxacin, was stopped after the identification of unacceptable toxicity (phototoxicity, hypoglycaemia, thrombocytopenia and nephritis).[6] In 1999, grepafloxacin was withdrawn from the market by the manufacturer because of cardiovascular effects, mainly prolongation of the QT interval.[11] In the same year, trovafloxacin was withdrawn in Europe because of 152 documented reports of serious liver toxicity, including nine patients who died or required a liver transplant.[12] The use of sparfloxacin was markedly limited because of phototoxicity and cardiotoxicity,[13] and in February 2001 the manufacturer withdrew the drug from the US market. The labelling of moxifloxacin, gatifloxacin, and levofloxacin has been modified by adding warnings about potential prolongation of the QT interval and disturbances of blood glucose (this last only for gatifloxacin).[13]

Various studies have demonstrated a correlation between certain adverse events and specific sites

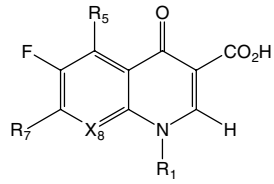

Fig. 1. The basic nucleus of the fluoroquinolones.

and constituents around the fluoroquinolone nucleus (figure 1).[14-16] It has been shown that position 1 controls genetic toxicity and theophylline interaction, which is most marked with enoxacin, pefloxacin and ciprofloxacin.[17] The carboxyl in position 3 and the keto group in position 4 are both involved in chelation and metal binding, and so influence the interactions of all fluoroquinolones with antacids, milk, iron and other preparations containing Ca^{2+} and Mg^{2+}. Position 7 controls γ-aminobutyric acid (GABA)-binding activity in the brain and is responsible for a number of CNS adverse effects, particularly convulsions; it is also involved in theophylline interactions. The fluoroquinolones more frequently associated with CNS adverse reactions are fleroxacin, trovafloxacin and grepafloxacin.[16] Position 8 has been shown to be the most important in mediating phototoxicity, with fluorine having more phototoxic potential than chlorine or nitrogen. A high degree of phototoxicity is associated with the dihalogenated quinolones, such as lomefloxacin, sparfloxacin and clinafloxacin. There is some suggestion that position 5 is also important for phototoxicity and QT prolongation.[18] Finally, hepatotoxicity has been found in the presence of two or three nitrogens in the molecule of quinolones (e.g. trovafloxacin).[6]

The overall incidence of adverse events associated with fluoroquinolone use in the US and Europe varies widely among the different fluoroquinolones, from 4.2% for ofloxacin to 47% for grepafloxacin.[5] Information concerning the true incidence of adverse drug reactions (ADRs) cannot be obtained by spontaneous reporting, since the events are always under-reported. However, when consumption data are available, comparing the toxicity profiles of the drugs in the same therapeutic class and with similar indications that are marketed in the same country in a comparable period of time is generally acceptable[19] because, under these conditions, the under-reporting can be assumed to be more or less of the same magnitude for the reference drugs.[20] Many comparative studies of the safety of different drugs on the basis of spontaneous reporting data have been published.[21-27]

Given the particular nature of the fluoroquinolone market and consumption in Italy, the aims of this study were to compare the adverse reactions of fluoroquinolones with those of other antibacterial drugs prescribed in three Italian regions and to investigate whether the spontaneous reporting data, correlated with sex and age of patients and with regional prescription data, reveal differences in toxicity profiles of individual fluoroquinolone antibacterial agents.

Methods

The data on fluoroquinolone antimicrobial agents currently available in Italy (figure 2), and on other systemic antimicrobials were obtained from a database containing all of the spontaneous reports of ADRs from the Italian regions of Emilia Romagna, Lombardy and the Veneto. These regions had an estimated population of about 18 million inhabitants in January 2000 (about 32% of the Italian population) and are the principal contributors to the Italian spontaneous surveillance system (accounting for about 54% of all Italian reports). We analysed the spontaneous reports collected between January 1999 and December 2001.

The following information was considered: reporter category, patient age and sex, the reporter's diagnosis of the ADR, the characteristics of the underlying disease, and drug exposure (indication, duration of treatment and dosage). The reports were classified according to the WHO criteria for

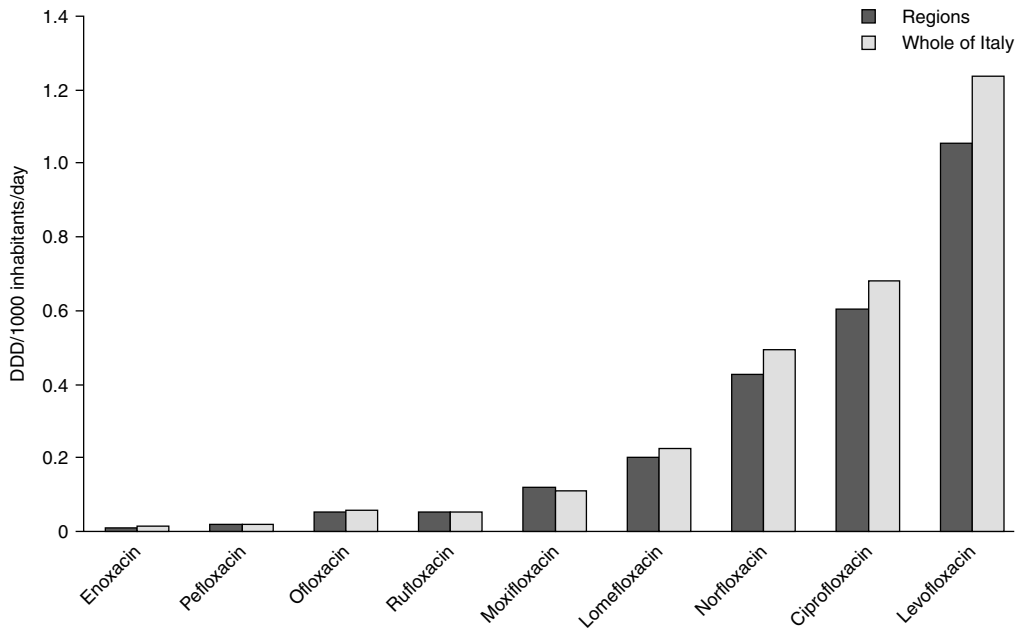

Fig. 2. Individual fluoroquinolone consumption in the Emilia Romagna, Lombardy and the Veneto regions compared with consumption in the whole of Italy during the study period. **DDD** = daily defined dose.

causality assessment,[28] and those with a certain, probable or possible causality assessment were included in the analysis. The drugs were categorised using the Italian Codifa System and the anatomical therapeutic chemical (ATC) classification. The reactions were coded according to the WHO Adverse Reaction Terminology (WHOART) and classified as serious or nonserious events on the basis of the WHO Critical Term List.[29]

All reports of ADRs occurring in association with fluoroquinolones during the study period were analysed in detail by a specially constituted *ad hoc* panel of experts that included internists, pharmacologists and pharmacists. The main task was to check the completeness of the reports and the terminology of the ADRs. The reports with two or more symptoms were reviewed by the team and a single diagnosis was formulated whenever possible. The reporting doctor was contacted if further clinical data were necessary to reach a diagnosis. The reports with no temporal correlation between drug exposure and disease onset, a doubtful ADR diagnosis or relating to events obviously due to the underlying disease were excluded.

Fluoroquinolone consumption in the three regions during the study period (figure 2) was derived from the regional databases holding all of the prescriptions of drugs (such as the fluoroquinolones) that are reimbursed by the Italian health system. Figure 2 also shows national consumption (kindly supplied by OsMed using IMS Health data), which has a similar pattern. Age- and sex-related consumption data (figure 3) were available only for Lombardy, but we think they are representative of the other two regions. Drug consumption was expressed as daily defined dose (DDD) per 1000 inhabitants per day.

For each drug the female/male reporting rate with 95% confidence intervals was calculated on the basis of gender distribution in the three regions. The toxicity profiles of fluoroquinolones were compared with one another and with other sys-

temic antimicrobials using the χ^2 test for statistical analyses. The same test has been used to compare the female/male reporting rate of individual fluoroquinolones.

Results

During the study period, 10 011 reports (33% serious) were received by the system (a mean annual reporting rate of approximately 185 per million inhabitants). A total of 1920 reports referred to systemic antimicrobials, of which 432 (22.5%) involved fluoroquinolones. Only seven reports were excluded by the expert panel, mainly because the dates of drug administration and/or reaction onset were missing. The analysis was therefore based on 425 reports of 621 reactions (about 1.5 per patient). In included reports, causality assessment was certain in 2%, probable in 76% and possible in 22%, with no significant differences among single fluoroquinolones.

The number of reports relating to individual fluoroquinolones is shown in table I. The female/male reporting rate ratio of 1.2 was lower than that observed for all other systemic antimicrobials (1.4); this can be explained by the higher fluoroquinolone consumption in males than females (figure 3), mainly due to levofloxacin (Lombardy data for individual drugs not shown). However, we observed a female/male reporting rate ratio significantly higher for rufloxacin and moxifloxacin than the other fluoroquinolones, even though their consumption was slightly greater among male patients.

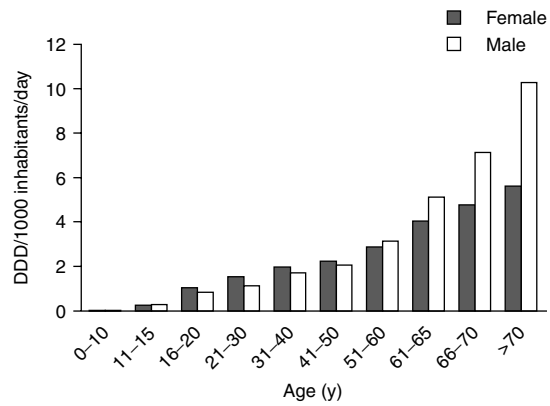

Fig. 3. Age- and sex-related fluoroquinolone consumption in the Lombardy population during the study period. **DDD** = daily defined dose.

Thirty-eight percent of the reports were sent by hospital doctors (7% by emergency rooms), 60% by general practitioners, and the remaining 2% by specialists and pharmacists. During the same period, 48% of the reports regarding other antibacterial drugs were reported by general practitioners

Table I. Adverse reaction reports attributed to the fluoroquinolones, available in Italy during the study period (January 1999–December 2001). Female/male reporting rate was calculated on the basis of gender distribution in the three Italian regions

Drug	No. of reports		Female/male reporting rate ratio (95% CI)
	total (% serious)	female/male	
Levofloxacin	164 (44.5)	77/87	0.84 (0.62–1.14)
Ciprofloxacin	115 (46.1)	68/47	1.37 (0.94–1.98)
Moxifloxacin[a]	42 (31.0)	30/10	2.83[b] (1.38–5.79)
Lomefloxacin	39 (51.3)	20/19	0.99 (0.53–1.86)
Norfloxacin	23 (39.1)	15/8	1.77 (0.75–4.18)
Pefloxacin	18 (35.0)	10/8	1.18 (0.47–2.99)
Rufloxacin	12 (33.3)	11/1	10.39[b] (1.34–80.45)
Ofloxacin[c]	8 (44.4)	3/4	0.71 (0.16–3.16)
Enoxacin	4 (25.0)	0/4	NA
Total	**425 (43.2)**	**234/188**	**1.18 (0.97–1.42)**

a In two reports sex was not reported.
b Significant differences (χ^2 test, $p < 0.01$).
c In one report sex was not reported.
NA = not applicable.

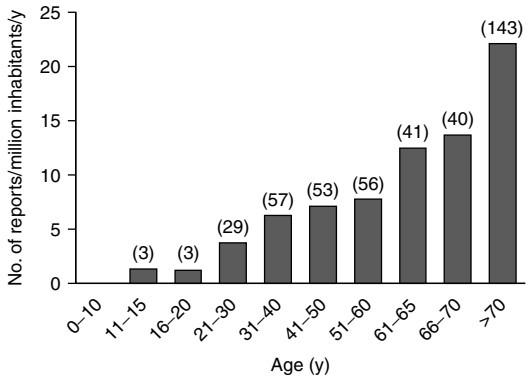

Fig. 4. Age-specific adverse fluoroquinolone reaction reporting rates per million inhabitants per year in the combined Emilia Romagna, Lombardy and the Veneto regions of Italy from January 1999 to December 2001. Numbers in parentheses are the numbers of reports for each specific age group.

and 46% by hospital doctors (5% by emergency rooms). On the basis of reporter categories, it was deduced that 31% of the fluoroquinolone reports involved inpatients and 69% outpatients. The fluoroquinolones were administered orally in 98% of cases, with only 2% being parenterally administered.

The age-specific reporting rate is shown in figure 4. The total annual reporting rate increased with age, suggesting that the elderly are more susceptible. On the other hand, older patients consumed more fluoroquinolones than younger ones (figure 3); thus, the observed age-dependent increase in reporting rate may reflect increase in drug consumption.

The reporting rate of reactions to fluoroquinolones per DDD per 1000 inhabitants per day is shown in figure 5: pefloxacin was associated with the highest reporting rate (982), followed by moxifloxacin (356), rufloxacin (221) and lomefloxacin (196). Considering only the serious reports, pefloxacin maintains the highest rate (382), followed by moxifloxacin (110), lomefloxacin (101) and ciprofloxacin (88).

Table II shows the observed ADRs according to the involved organ systems. The most frequently reported reactions to fluoroquinolones involved the skin, but their percentage was significantly lower ($p < 0.01$) than that of other systemic antimicrobials. On the contrary, the percentages of reactions involving the CNS and musculoskeletal and psychiatric systems were significantly higher ($p < 0.01$). The individual drugs had a different pattern: the percentage of cutaneous reactions was significantly higher ($p < 0.01$) for ciprofloxacin; the percentage of musculoskeletal reactions was significantly higher ($p < 0.01$) for levofloxacin and pefloxacin; and the percentage of psychiatric reactions was significantly higher ($p < 0.05$) for rufloxacin. No significant differences have been found in ADRs involving the other system organ classes.

The most frequently reported serious reactions to fluoroquinolones were tendon disorders (16 reports, with 12 Achilles tendon ruptures), hallucinations (15), angioedema (11) and photosensitivity reactions (9). Eleven men and five women experienced serious tendinitis (median age 72, range

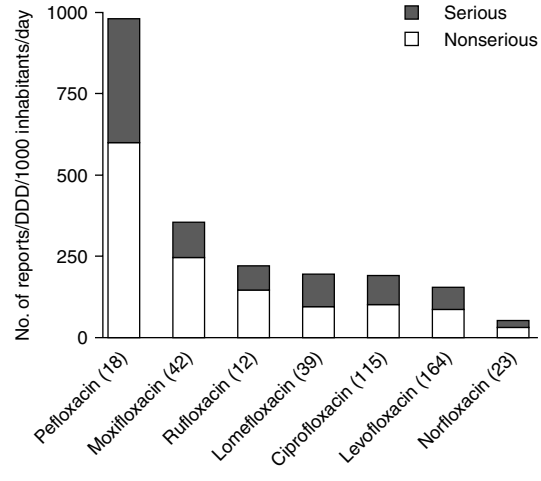

Fig. 5. Reporting rates of serious and nonserious reactions (coded according to the WHO Critical Term List) to fluoroquinolones per daily defined dose (DDD) per 1000 inhabitants per day in the combined Emilia Romagna, Lombardy and the Veneto regions of Italy. Only drugs with at least ten reports are included. Consumption figures are derived from regional prescription data. Numbers in parentheses are the total number of reports.

33–80, years); in five cases (31%), corticosteroids were concomitant drugs. Levofloxacin is associated with the highest rate (11.4 reports/daily defined dose/100 inhabitants/day) of serious tendinitis (figure 6). No reports on tendon disorders were associated with enoxacin, ofloxacin, rufloxacin, pefloxacin or moxifloxacin. The drugs with the largest number of hallucination reports were rufloxacin (5) and levofloxacin (5), whereas six of the nine cases of phototoxic reactions were attributed to lomefloxacin. During the study period, there were four cases of acute renal impairment, two cases of toxic epidermal necrolysis and two of Stevens-Johnson syndrome: all referred to ciprofloxacin. Three cases of international normalised ratio (INR) prolongation due to an interaction between warfarin and levofloxacin were also reported. We found 17 reports of rhythm disorders, mostly nonserious reactions such as tachycardia and palpitation; no torsade de pointes, ventricular tachycardia or atrial fibrillation were reported.

Table II will go here

Discussion

The data emerging during the clinical development of a new drug are not sufficient to assess its potential toxicity when it is used in a larger patient population.[30] The postmarketing period is therefore important for consolidating drug safety profiles and detecting previously unknown adverse effects.

Spontaneous reporting of ADRs has proved to be valuable in providing information about new drug-related adverse effects and generating early signals, and thus maintains a primary role among pharmacovigilance methods.[31,32] Through the analysis of spontaneous reports it is not possible to obtain the true incidence of adverse effects; however, the educational role of this type of data should not be disregarded. In fact, when the drug consumption data are available and the reporting rate is acceptable, we have the opportunity to learn more about the safety of a group of drugs, as from studies on nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors

Table II. Adverse effect profiles of fluoroquinolones[a] by body system in comparison with the profiles of other systemic antimicrobials. Number of reports with, in parentheses, the percentage of all reported reactions within each group

Organ or system	Levofloxacin	Ciprofloxacin	Moxifloxacin	Lomefloxacin	Norfloxacin	Pefloxacin	Rufloxacin	Total for all fluoroquinolones	Total for other systemic antimicrobials
Skin	46 (19.9)	53 (34.9)[b]	10 (13.5)	17 (27.9)	11 (36.7)	8 (25.8)	5 (23.8)	150 (25.0)[c]	1074 (58.5)
Musculoskeletal	59 (25.5)[b]	9 (5.9)	1 (1.4)	6 (9.8)	3 (10.0)	7 (22.6)[b]	2 (9.5)	87 (14.7)[c]	5 (0.3)
CNS	24 (10.4)	16 (10.5)	17 (23.0)	8 (13.1)	1 (3.3)	3 (9.7)	4 (19.0)	73 (12.2)[c]	66 (3.6)
Gastrointestinal	18 (7.8)	16 (10.5)	12 (16.2)	6 (9.8)	3 (10.0)	3 (9.7)	2 (9.5)	60 (10.0)	167 (9.1)
Body as a whole	26 (11.3)	11 (7.2)	9 (12.2)	7 (11.5)	5 (16.7)	1 (3.2)		59 (9.8)	136 (7.4)
Psychiatric	15 (6.5)	13 (8.6)	9 (12.2)	7 (11.5)	3 (10.0)	4 (12.9)	6 (28.6)[d]	57 (9.3)[c]	33 (1.8)
Cardiovascular	7 (3.0)	7 (4.6)	8 (10.8)	2 (3.3)		3 (9.7)	1 (4.8)	28 (4.7)	64 (3.5)
Others[e]	36 (15.6)	27 (17.8)	8 (10.8)	8 (13.1)	4 (13.3)	2 (6.5)	1 (4.8)	86 (14.3)	292 (15.9)
Total[f]	231 (100)	152 (100)	74 (100)	61 (100)	30 (100)	31 (100)	21 (100)	600 (100)	1837 (100)

a With at least ten reports in the considered period.

b Significant differences (χ^2 test, $p < 0.01$) among the fluoroquinolones in the reports implicating this organ system versus the other reports.

c Significant differences (χ^2 test, $p < 0.01$) among total fluoroquinolones and the other systemic antimicrobials in the reports implicating this organ system versus the other reports.

d Significant differences (χ^2 test, $p < 0.05$) among the fluoroquinolones in the reports implicating this organ system versus the other reports.

e None of the other organ systems involved accounted for more than 4% of the fluoroquinolone reports.

f The total number of reports is higher than that given in the text and table I because the same report may contain multiple system reactions.

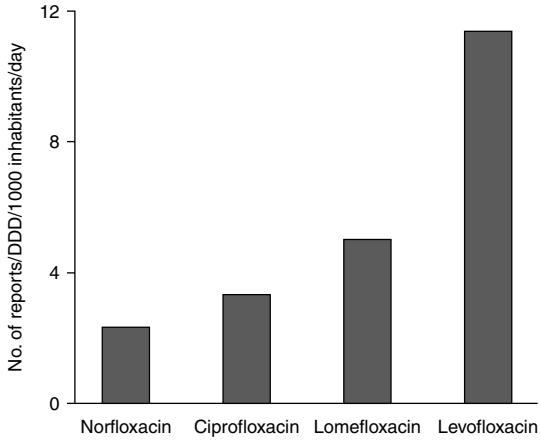

Fig. 6. Reporting rates of serious fluoroquinolone-related tendinitis per daily defined dose (DDD) per 1000 inhabitants per day in the combined Emilia Romagna, Lombardy and the Veneto regions of Italy. Consumption figures are derived from regional prescription data.

and antihistamines, published in Spain, Italy, Sweden and the UK.[21,22,24-26]

In the case of fluoroquinolones, spontaneous reporting played a considerable role, as some drugs have been withdrawn from the market on the basis of reports of serious ADRs. The recent 'cerivastatin case' further emphasises that spontaneous reporting is able to detect different toxicity profiles of drugs in the same chemical-therapeutic class.

The fluoroquinolones are widely used antibacterial agents in Italy,[33] with levofloxacin ranking first despite its recent introduction (1998). Other peculiarities of the Italian market are the presence of rufloxacin and the low ofloxacin consumption.

The age-related increase in reporting rates essentially reflects the greater use of fluoroquinolones in older patients, thus confirming that the incidence of adverse effects is not higher in the elderly than in the younger population.[34]

Compared with published data for other drug classes,[35-40] fluoroquinolones have a lower female/male reporting rate ratio, possibly because of their greater use (particularly levofloxacin) in male patients aged over 60 years. It is known that chronic obstructive pulmonary disease, one of the main indications for fluoroquinolone use in Italy, is more prevalent in men than in women aged over 60 years.[41]

When adjusted for drug prescriptions, our data suggest higher reaction rates for pefloxacin and moxifloxacin. As moxifloxacin is the newest fluoroquinolone on the Italian market (launched in 2000), we presume that the larger number of reports is due to doctors paying particular attention to ADRs according to the reporting guidelines. On the contrary, the lower reporting rate for norfloxacin (the oldest marketed fluoroquinolone) could be due to a drop in attention.

Adverse events involving the CNS are, after gastrointestinal reactions, the second most frequently reported form of fluoroquinolone toxicity in the literature. Their overall incidence is 1–2% (ranging from 0.2 to 11% for individual agents), and they include a broad range of effects, such as dizziness, mild headache and drowsiness, followed by insomnia, organic psychosis and convulsions.[42]

Our spontaneous reporting data confirm that, unlike that of other antimicrobials, fluoroquinolone toxicity has the CNS as an important target organ. The proportion of CNS-related reactions and psychiatric disorders (generally considered together by other authors) is about 22%, very similar to the approximately 23% found in the database of the WHO Collaborating Centre in Uppsala (data on file). NSAIDs or theophylline were concomitant drugs in 12% of the patients experiencing CNS reactions with fluoroquinolones. Rufloxacin and moxifloxacin were associated with a higher proportion of CNS adverse reactions than other fluoroquinolones. Clinical studies have found that the degree of the CNS reactions induced by moxifloxacin is similar to that of the reactions induced by norfloxacin, but higher than those of the reactions induced by ciprofloxacin, ofloxacin or levofloxacin.[42] The few clinical data available for rufloxacin confirm that CNS-related events are the

most frequently reported.[43] The drug diffuses efficiently into the cerebrospinal fluid and it is likely that the blood-brain barrier penetration of fluoroquinolones plays an important role in CNS toxicity.[14] However, some data have raised doubts about the possibility that the CNS reactions induced by fluoroquinolones are related to their lipophilicity.[43,44]

In our study, rufloxacin-related CNS events were more frequent in women, which explains the highest female/male reporting ratio for this agent. Recent trovafloxacin data have shown that CNS reactions occur more frequently in women than in men, although the reason for this is unknown.[42,45]

Skin reactions are the most frequently reported clinical manifestations related to systemic antimicrobials in the context of our spontaneous surveillance system, accounting for about 58% of all reported adverse events. This may reflect the over-reporting of skin reactions *per se* or the under-reporting of other organ reactions, but the latter is the more likely explanation because it is easier to recognise and report cutaneous adverse reactions than those involving other organ systems. The skin is also the main organ system involved in ADRs to fluoroquinolones, but the percentage is lower (25%) because of their different ADR pattern.

Clinical data show that fluoroquinolone-related skin reactions occur in about 0.5–3.0% of patients[46] and that they may be mediated by an allergic reaction or photosensitivity (both photoallergy and phototoxicity).

In our analysis, the highest proportion of photosensitivity reactions was reported in association with lomefloxacin. In animal and *in vitro* models, lomefloxacin seems to be the marketed fluoroquinolone that has the greatest potential for inducing phototoxic reactions[47,48] and, in a randomised clinical trial, the frequency of photosensitivity attributed to the drug was about 1%.[49] It has been suggested that an evening administration strategy could reduce the risk of inducing phototoxic effects.[50]

The most important cardiac toxicity of fluoroquinolones is prolongation of the QT interval. This has been recorded with the newer fluoroquinolones, and appears to be a class effect.[51] A recent prescription event monitoring study of the older fluoroquinolones confirmed this observation, by finding that ciprofloxacin was associated with the highest number of dysrhythmic cardiovascular events.[52]

In our database three serious rhythm disorders were associated with levofloxacin, one with moxifloxacin and one with pefloxacin; however, the data are not sufficient to reveal any particular differences among the individual fluoroquinolones in terms of cardiovascular toxicity.

Musculoskeletal adverse reactions are an important fluoroquinolone class effect. In our study, and in line with the WHO database, a higher proportion of these events was reported for levofloxacin and pefloxacin. In animal studies, all of the fluoroquinolones have induced arthropathy with cartilage erosions and noninflammatory effusions in juvenile animals,[53] and so fluoroquinolones are not approved for paediatric use or during pregnancy. A number of case reports and spontaneous report studies of fluoroquinolone-associated tendinitis have been published.[54-65] A retrospective cohort study found that the adjusted relative risk of Achilles tendinitis during fluoroquinolone use was 3.7 and that of other types of tendinitis 1.3.[66] More than 2000 tendon disorders have so far been reported worldwide to the WHO Collaborating Centre in Uppsala (data on file). A simultaneous increase in nontraumatic tendon rupture (mono- or bilateral) and in fluoroquinolone use has been observed in The Netherlands,[67] but the authors only partially attributed the tendinitis increase to fluoroquinolone use. A very recent nested case-control study among users of fluoroquinolones in a UK general practice database indicated that the overall excess risk of Achilles tendon disorders is 3.2 cases per 1000 patient years. This effect seems to be restricted to current users aged 60 years or older with a crude relative risk of 3.5

(95% CI 2.3–5.3).[68] Other possible risk factors for tendinitis include concomitant corticosteroid use, renal disease, haemodialysis and transplantation.[5]

In our analysis, levofloxacin was the fluoroquinolone with the highest tendinitis reporting rate, an observation that is supported by the WHO database, in which levofloxacin ranked first for tendinitis reports during the same period (522 including tendon disorder and rupture). A large number of tendinitis reports with levofloxacin have recently been observed in France. Subsequently, a 'Dear Doctor' letter was sent out in France, Germany and Italy informing of the levofloxacin-related risk of tendinitis, particularly in elderly patients and those receiving concomitant corticosteroids.

Fluoroquinolone nephrotoxicity is uncommon and may be a result of direct damage or a hypersensitivity response. The most common renal adverse effects are crystalluria, haematuria, interstitial nephritis and acute renal failure, particularly with ciprofloxacin.[69,70] In accordance with these data, we received reports of four cases of acute renal failure due to ciprofloxacin.

It has been reported that the effects of oral anticoagulants are enhanced by the concurrent administration of quinolones, although the mechanism underlying this possible interaction is unknown. A number of case reports have indicated that ciprofloxacin prolongs prothrombin times or increases INR in patients receiving warfarin anticoagulation therapy.[71-75] It seems that ciprofloxacin-warfarin coagulopathy is most prevalent in elderly patients who require multiple drug therapy;[76] there are also some case reports describing this interaction in the case of norfloxacin, ofloxacin and more recently levofloxacin.[77-80] The levofloxacin prescribing information leaflet in the US indicates the possible interaction with warfarin, but not that in the European Union.

Conclusion

The spontaneous reporting of ADRs has proved to be valuable in providing information about new drug-related adverse effects and generating early signals, thus maintaining its primary role among pharmacovigilance methods. It does not allow the risk associated with a given drug to be accurately quantified because of the possibly confounding bias and under-reporting of ADRs. Nevertheless, when an adequate reporting rate and consumption data are available, spontaneous reporting allows comparison of drug toxicity profiles within the same chemical-therapeutic class.

The analysis of the Emilia Romagna, Lombardy and Veneto databases of spontaneous ADR reporting confirms that, unlike that of other systemic antimicrobials, the toxicity of fluoroquinolones often involves the CNS and musculoskeletal system. Furthermore, the individual fluoroquinolones have different safety profiles: ciprofloxacin was more often associated with skin reactions than other fluoroquinolones, levofloxacin and pefloxacin with musculoskeletal disorders and rufloxacin with psychiatric disorders. Our spontaneous reporting data show that levofloxacin was the fluoroquinolone with the highest rate of serious tendon disorders, phototoxic reactions were more frequent with lomefloxacin, and toxic epidermal necrolysis and Stevens-Johnson syndrome were were reported only with ciprofloxacin. These findings should be taken into account when prescribing a fluoroquinolone to individual patients.

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