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Safety Profile of the Fluoroquinolones

Analysis of Adverse Drug Reactions in Relation to Prescription Data Using Four Regional Pharmacovigilance Databases in Italy

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Abstract

Background: Fluoroquinolones are widely used both in primary care and in hospital settings. Since the last comparison performed in Italy on the safety profiles of different fluoroquinolones, a new molecule, prulifloxacin, has been introduced into the market and several warnings concerning this class of drugs have been released. The aim of this study was to reassess the safety profiles of fluoroquinolones using the database of the Italian Interregional Group of Pharmacovigilance (IGP) and the administrative data of fluoroquinolone prescriptions.

Methods: All adverse drug reactions (ADRs) reported in four Italian regions (Lombardy, Veneto, Emilia Romagna and Tuscany) were retrieved from the IGP database. Consumption data (defined daily dose [DDD]/1000 inhabitants/day) were used as denominators. Both single reports and all ADRs (classified by System Organ Classes and MedDRA® Preferred Term [PT]) due to fluoroquinolones were considered as numerators of each analysis, comparing two periods (2005 vs 2006). All fluoroquinolones with at least ten reports per year were included in the analysis.

Results: On the basis of 272 reports (532 single ADRs or PTs), patients did not show any statistically significant differences between 2005 and 2006 in terms of sex, age and number of concurrent medications. After adjustment for drug consumption, moxifloxacin showed the highest reporting rate (84.6 reports/DDD/1000 inhabitants/day; 15.4 serious reports/DDD/1000 inhabitants/day) followed by prulifloxacin (72.2; 22.2 serious) and levofloxacin (55.3; 30.6

serious) in 2005. An increment of ADR/report rates was observed over the 2 years for all fluoroquinolones except prulifloxacin, which had the lowest ADR reporting rate in 2006 (25.0; 12.5 serious). In 2006, the rate of serious ADRs associated with prulifloxacin was lower than with ciprofloxacin, while in 2005 serious events were almost equal for both compounds (55.6 vs 47.6 serious ADRs/DDD/1000 inhabitants/day). Ciprofloxacin showed the highest proportion of cutaneous PTs (e.g. rash, exanthema). Tendinopathies were mainly due to levofloxacin.

Conclusions: These data suggest that different fluoroquinolones are characterized by different rates and types of ADRs. Among them, prulifloxacin was associated with more ADRs than other fluoroquinolones in 2005 but with fewer ADRs in 2006, when its consumption increased. Although these findings may represent an encouraging perspective towards a more appropriate use of fluoroquinolones because of their individual safety profiles, further pharmacoepidemiological studies must be performed to substantiate these results.

Background

Because of their broad spectrum of activity, fluoroquinolones are widely used in primary care and hospital settings. In Italy, fluoroquinolones ranked third (levofloxacin) and fifth (ciprofloxacin) in consumption among antibacterials in 2004 through to 2007,[1-4] with an increasing rate of about 4% per year between 2004 and 2007. While the efficacy of these drugs has improved from the first- (e.g. nalidixic acid) to the third-generation (e.g. moxifloxacin), their benefit-risk profile still needs careful evaluation. While chemical modifications introduced into the pharmacophore (bicyclic quinolone nucleus) have provided expanded activity against serious infections due to *Streptococcus pneumoniae*, other functional groups are responsible for potentially serious adverse drug reactions (ADRs). For instance, a fluorine atom in position 8 is a strong predictor of phototoxicity, while methylpiperazinyl groups in position 7 lead to neuropsychiatric ADRs because of binding to GABA receptors in the brain.[5] Furthermore, because of serious ADRs, such as drug-induced hypo- or hyperglycaemia (gatifloxacin), corrected QT (QTc) interval prolongation and torsades de pointes (gatifloxacin, sparfloxacin), the safety profile of some fluoroquinolones has been recently reviewed, and some molecules have been withdrawn from the European market (temafloxacin, gemifloxacin).[5-8] Postmarketing investigations and spontaneous reporting have been instrumental in these regulatory decisions. Indeed, premarketing studies are unable to detect all the possible types of ADRs, especially rare events. Despite its well recognized limits, spontaneous reporting has the capability of providing a general overview of all types of ADRs, thus allowing the comparison among different molecules of the same pharmacological class with similar indications of use. To this purpose, a previous article of ours[9] compared the safety profiles of fluoroquinolones using ADR reports after being adjusted for consumption data. In that study, pefloxacin had the highest ADR reporting rate followed by moxifloxacin, rufloxacin and lomefloxacin. Skin reactions were significantly higher for ciprofloxacin, while musculoskeletal and psychiatric ADRs were more frequent for levofloxacin, pefloxacin and rufloxacin.[9]

Such information can be crucial in helping physicians to select the right drug for individual patients according to its peculiar predisposing factors to ADR development among many agents of the same class.

Since 2003, no further studies comparing the safety profiles of fluoroquinolones have been conducted in Italy or in other Western countries.

During these years the Italian Pharmacovigilance system has significantly improved, and the Italian Interregional Group of Pharmacovigilance (IGP)[10] now accounts for more than 50% of ADR reporting in Italy. Moreover, a new fluoroquinolone, prulifloxacin, was introduced into the Italian market in 2004[11] so we thought it important to review the data on ADRs concerning all the commercially available fluoroquinolones in Italy.

Although several nonserious adverse events due to prulifloxacin, including nausea, gastric pain, pruritus, diarrhoea and dyspepsia, have been reported during clinical trials,[12] only two case reports on the 'probable' association between prulifloxacin and exacerbation of myasthenia gravis[13] and occurrence of kidney failure[14] have recently been published. This safety profile is comparable to that reported in premarketing studies for all fluoroquinolones.[12]

In this context, a new pharmacoepidemiological evaluation of the safety aspects of fluoroquinolones was conducted using the database of the Italian IGP in order to update safety data and to evaluate the possible differences, in terms of ADR rates and types, between new and older fluoroquinolones.

Methods

As already stated above, spontaneous reports cannot be used to estimate ADR rates because of underreporting bias. However, when consumption data are available, comparing the tolerability of drugs within a therapeutic class having similar indications is considered acceptable because, under these conditions, the underreporting phenomenon can be assumed to be of the same magnitude for all drugs under study.[15]

To conduct such an analysis, all ADRs due to fluoroquinolones (Anatomical Therapeutic Chemical [ATC] class J01MA) reported in four Italian regions (Lombardy, Veneto, Emilia Romagna and Tuscany) from 1 January 2005 to 31 December 2006 were retrieved from the database of the Italian IGP. These regions cover about 33% of the Italian population, with a total of about 18 million inhabitants. In total, until December 2006 the IGP included 45 673 reports, representing more than half of all ADRs reported in Italy. All reports were analysed by an expert committee composed of internists, pharmacologists and pharmacists, who checked the completeness of the reports, terminology of the ADRs and the codification procedures that had been applied by each healthcare authority using the Medical Dictionary for Regulatory Activities (MedDRA®).[16] Whenever possible, reports with two or more symptoms were coded to a single diagnosis.

Only ADRs considered 'certain', 'probable' or 'possible' on the basis of WHO criteria[17] were included in the analysis. Fluoroquinolones and ADRs were coded according to the ATC classification and MedDRA® thesaurus, respectively.[18] The degree of severity (ADRs leading to hospitalization, increased length-of-stay, disability or death) was assessed on the basis of the WHO Critical Term List.[19]

Consumption data, expressed in defined daily dose (DDD)/1000 inhabitants/day, were drawn from administrative databases of the same regions. Both single reports and all ADRs (also considered as single Preferred Terms [PTs] according to MedDRA® hierarchy) due to fluoroquinolones were considered as the numerator of each analysis. The comparison between 2005 and 2006 was adopted to take into account the possible Weber effect[20,21] due to the recent introduction of prulifloxacin (21 June 2004[11]) into the market, as well as to evaluate the increment over time of the ADR rate for each fluoroquinolone. Furthermore, a molecule was included in the analysis whenever it accounted for at least ten adverse events in either study year.[9]

Statistical Analysis

The patients' characteristics, including age and number of concurrent medications, were reported in tertiles. To compare all patients' variables between 2005 and 2006, the chi-squared test was used; a p-value of <0.05 was considered statistically significant.

Results

Overall, 272 reports (532 single ADRs or PTs; on average 1.9 PTs per patient according to

MedDRA® classification) of adverse reactions to fluoroquinolones were observed during the study period: 112 in 2005 and 160 in 2006. Among them, 99 events were serious (36.4%): of these, three cases (3.0%) were fatal, 75 events (75.8%) caused hospitalization or increased the length of hospital stay, 6 (6.1%) resulted in disability and 15 (15.2%) were defined as life-threatening. The events were reported by hospital physicians (110), general practitioners (106), specialists (6), pharmacists (7) and nurses (6). Thirty-seven reports did not state the reporters' origin.

In the majority of cases, ADRs were 'possible' (187) according to causality assessment; most patients were females (149) and elderly (mean age 61.0 ± 19.7 years). Only one case involved two fluoroquinolones as the cause of the adverse event. The route of administration was oral in 209 cases (76.8%), intravenous in 21 (7.7%) and not specified in the remaining 42 cases (15.4%).

As shown in table I, patients did not show any statistically significant differences between the 2 years of the study in terms of sex, age or number of concurrent medications.

With regard to ADRs for the individual fluoroquinolones, the highest number of events was for levofloxacin in 2005 (total/serious = 47/26) and 2006 (77/43), followed by moxifloxacin (22/4 in 2005; 39/30 in 2006), ciprofloxacin (22/12 in 2005; 31/16 in 2006) and prulifloxacin (13/4 in 2005; 8/4 in 2006) [figure 1]. Consumption data were almost equal in 2005 and 2006 except for prulifloxacin (0.18 vs 0.32 DDD/inhabitants/day) [figure 2]. After adjustment for drug consumption data, moxifloxacin ranked first in the number of ADRs (84.6 reports/DDD/1000 inhabitants/day; 15.4 serious events/DDD/1000 inhabitants/day) followed by prulifloxacin (72.2; 22.2 serious) in 2005. However, in 2006, moxifloxacin (150.0; 115.4 serious) ranked first followed by levofloxacin (89.5; 50.0 serious) and ciprofloxacin (49.2; 25.4 serious), while prulifloxacin (25.0; 12.5 serious) was in last place for ADRs (figure 3). These findings were almost the same when the analysis was conducted for PTs. In both analyses, prulifloxacin showed, in contrast to the other molecules, a decrease in ADR rate in 2006 in comparison with 2005, when it ranked first in terms of total

Table I. Patient characteristics in fluoroquinolone adverse reaction reports in 2005 vs 2006

Variable	2005 (n = 112) [n (%)]	2006 (n = 160) [n (%)]	p-Value
Sex[a]			0.725
Male	49 (43.7)	73 (45.6)	
Female	63 (56.3)	86 (53.8)	
Age strata[b]**(y)**			0.546
11–53	39 (34.8)	53 (33.1)	
54–73	33 (29.5)	57 (35.6)	
74+	40 (35.7)	50 (31.3)	
Concurrent medication strata[b]			0.360
0	50 (44.6)	84 (52.5)	
1–2	26 (23.2)	36 (22.5)	
3+	36 (32.1)	40 (25.0)	
Patient status			0.408
Outpatient	70 (62.5)	92 (57.5)	
Inpatient	42 (37.5)	68 (42.5)	
Imputability			0.723
Certain	2 (1.8)	3 (1.9)	
Probable	30 (26.8)	50 (31.3)	
Possible	80 (71.4)	107 (66.9)	

a One case report in 2006 did not state the patient's sex.

b Strata are reported in tertiles.

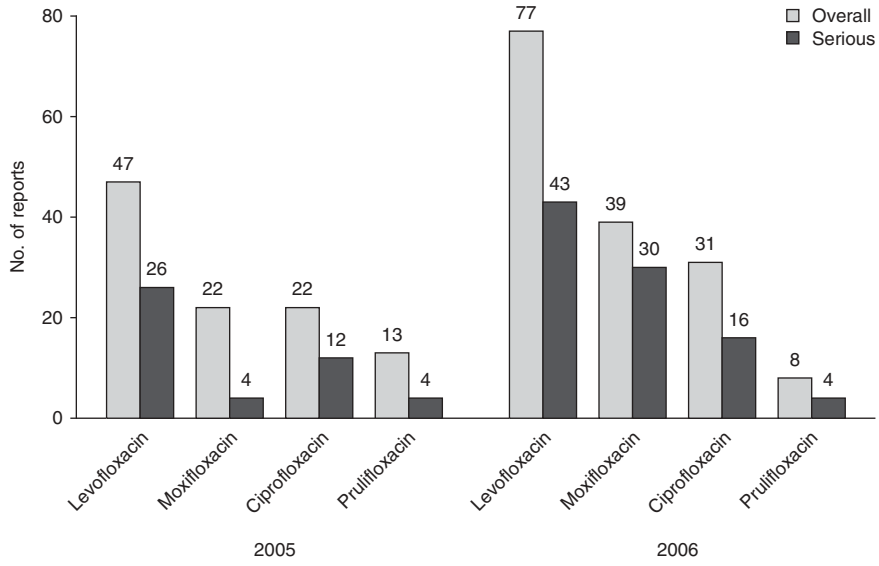

Fig. 1. Numbers of adverse drug reaction reports for each of the fluoroquinolones in 2005 and 2006, shown as overall numbers and numbers of serious reactions.

ADRs (155.6 ADRs/DDD/1000 inhabitants/day) [figure 4].

The types of adverse events are shown in tables II and III according to System Organ Class (SOC) and PT classifications from the MedDRA®, respectively. Skin reactions were the most frequently reported, with levofloxacin showing the highest number of ADRs in this SOC category as well as the musculoskeletal and respiratory categories (table II).

Grouping MedDRA® PTs with the same clinical meaning, five categories demonstrated more than ten occurrences (table III). Ciprofloxacin had the highest proportion of cutaneous PTs (rash exanthema, erythema, urticaria), while other allergic events (anaphylactic shock, dyspnoea) were more frequent for levofloxacin and moxifloxacin. Achilles tendon rupture and other tendinopathies were mainly due to levofloxacin. Finally, according to the PT classification, no cardiac or hepatic adverse effects reached ten reports for any of the fluoroquinolones.

Discussion

To our knowledge, this is the first study aimed at comparing the safety profiles of fluoroquinolones, including prulifloxacin, the most recently marketed molecule belonging to this class. Over the 2 years of the study, moxifloxacin had the highest ADR reporting rate when adjusted for drug consumption, while in terms of single ADRs (or PTs) it showed the highest rate in 2006. As far as ADR seriousness is concerned, prulifloxacin showed an analogous safety profile to that of ciprofloxacin in 2005. Nevertheless, the total and serious event rates for prulifloxacin sharply decreased in 2006.

These results are the only ones to be provided after the study of Leone et al.,[9] whereas fluoroquinolone prescribing in Italy has increased by about 4% between 2004 and 2007.[1-4] When compared with previous findings[9] our data show that moxifloxacin remains one of the fluoroquinolones with the highest ADR rate. On the other hand, pefloxacin, rufloxacin, lomefloxacin and norfloxacin were excluded from our analysis, since they were not able to reach ten reports or PTs in 2005 or 2006. Exclusion of these molecules was probably due to the different time period used in the current investigation, namely 2 years instead of 3, as in the previous study.[9]

It is worth noting that, although no 'Dear Doctor' letter or any other specific Drug Authorities

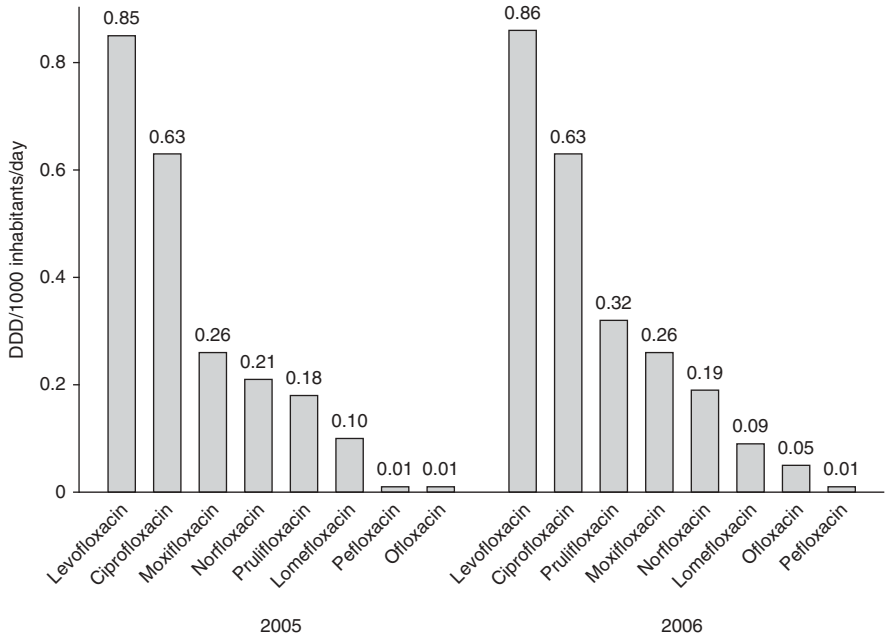

Fig. 2. Consumption data for individual fluoroquinolones expressed as defined daily doses (DDD)/1000 inhabitants/day in 2005 and 2006.

Alert was issued within the 2-year study, the reporting rate of ADRs increased for all fluoroquinolones other than prulifloxacin. An explanation for this phenomenon can be accrued from the establishment of several Italian regional centres of pharmacovigilance according to a new national regulation,[22] which resulted in a general increase in Italian ADR reporting rates.[10] In addition, the reduction in ADR rate of the newly marketed prulifloxacin[11] can be partly explained by the Weber effect,[20,21] an epidemiological phenomenon observed whenever a drug is marketed, consisting of a reduction in ADR reporting rate despite a continued growth in prescribing. Although the Weber effect has still not been clarified for certain medications, a decrease in prulifloxacin reports/ADRs was observed over the 2 years under study, despite an increasing prescription rate.

The fact that moxifloxacin showed the highest rate of ADRs is in keeping with our previous study.[9] However, a recent review suggests that when moxifloxacin is used strictly according to the guidelines, cutaneous, gastrointestinal and neurological adverse events are less frequent than with other antibacterials (macrolides, telithromycin and sulfonamides) used for respiratory infections.[23]

Another possible explanation for these findings might be related to the 'confounding by severity' bias. Indeed, moxifloxacin is mainly used for Gram-positive infections, ciprofloxacin and prulifloxacin for Gram-negative infections, and levofloxacin for both types of infections. In other words, the better safety profile of prulifloxacin could be partly explained by its use in patients with less propensity to develop ADRs.[24]

In our study, the type of events being reported was generally in line with the medical literature. According to SOC classification, skin events were most frequently associated with ciprofloxacin, and musculoskeletal and respiratory events with levofloxacin and prulifloxacin.[5,25]

When looking only at PTs, a higher proportion of fluoroquinolone-associated tendonitis was reported for levofloxacin, in keeping with a previous pharmacovigilance study, as well as the WHO database.[9]

When compared with the effects of other antibacterials, tendinopathy seems to be a peculiar

class effect due to fluoroquinolones,[26,27] although an association has also been raised for trimethoprim and sulfonamides.[27] In this regard, some epidemiological investigations show an adjusted relative risk of 3.7 for Achilles tendonitis during fluoroquinolone use and of 1.7 for the other types of tendonitis, whereas an estimated incidence range of tendon rupture of 0.14–0.4% is reported.[9,25] This number may be higher in patients with well known risk factors, chiefly represented by age >60 years, intense athletic activities and concurrent use of corticosteroids. Other risk factors include renal failure, renal transplantation, haemodialysis, diabetes mellitus, gout, hyperparathyroidism, and rheumatic and peripheral vascular diseases.[7,8,25,28]

The hypothesized mechanism of tendonitis due to fluoroquinolones is complex and poorly understood. Preclinical data indicated the methylpiperazinyl substituent in position 7 as a possible leading cause of tendonitis, suggesting direct toxic activity on the tendons. Another hypothesis suggests that fluoroquinolone use might enhance the formation of reactive oxygen species that subsequently cause tendon damage. Tendon rupture may occur whenever a patient has risk factors such as age >60 years or concomitant corticosteroid use, which can impede tendon repair.[7,8,25]

According to current medical literature,[29-31] the incidence of serious allergic reactions due to fluoroquinolones, taken as a class, seems to be similar to that for penicillins, and even lower than that for cephalosporins. In particular, skin ADRs as well as anaphylactic shock are considered type I IgE-mediated reactions. Levofloxacin and moxifloxacin were the molecules mainly involved, and other previous analyses of the IGP database indicated that moxifloxacin had a major association with this type of event.[10] From a clinical viewpoint, the problem of fluoroquinolone choice for the treatment of infective diseases is related to cross-reactivity phenomena that can provoke anaphylactic reactions. Unfortunately, skin testing has been considered to be poorly reliable because of false-positive results collected among healthy control subjects. A direct release of histamine caused by fluoroquinolones may lead to anaphylactoid reactions, thus increasing the unpredictability of such ADRs. On the whole, given the fact that fatal allergic events can occur, fluoroquinolones

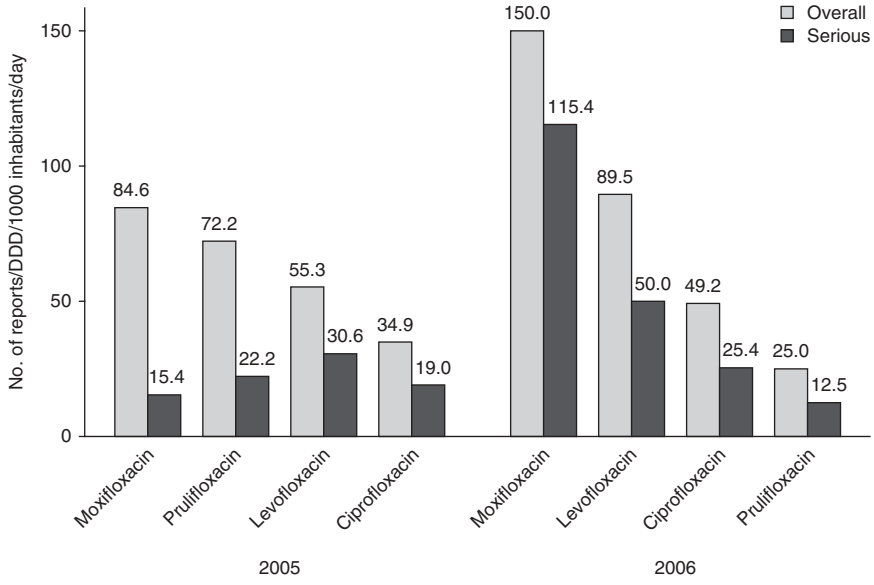

Fig. 3. Numbers of adverse drug reaction reports for each of the fluoroquinolones adjusted for drug consumption in 2005 and 2006. **DDD** = defined daily dose.

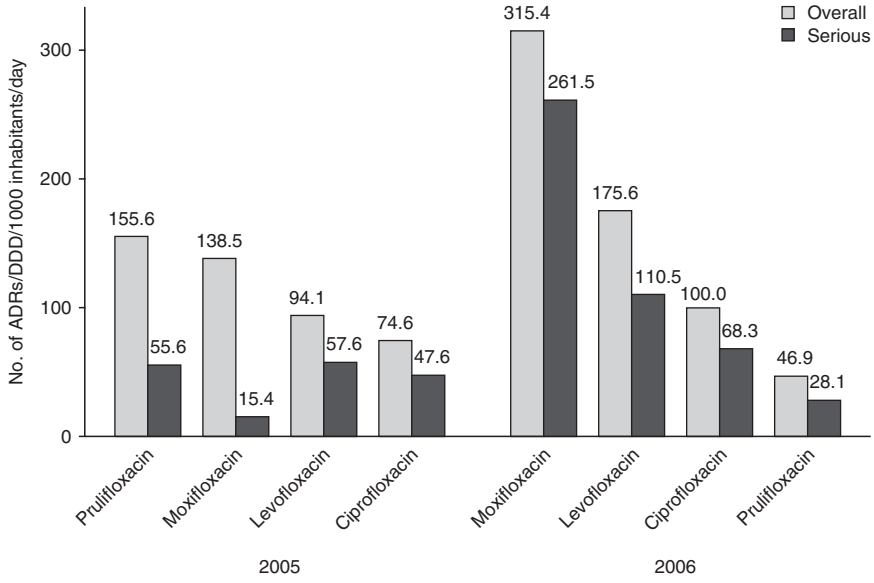

Fig. 4. Numbers of single adverse drug reactions (ADRs) [or preferred terms] for each of the fluoroquinolones adjusted for drug consumption in 2005 and 2006. **DDD** = defined daily dose.

continue to be contraindicated in patients who exhibit a positive history of allergy.[8]

Some differences were also found for other SOC categories, in which prulifloxacin showed a higher proportion for respiratory and nervous system ADRs when compared with ciprofloxacin. The low number (<10 ADRs) of these observations makes any conclusion impossible. This also applied to other kinds of PTs such as metabolic, heart or neuropsychiatric events.[7,32] However, when the most frequent SOCs and PTs are considered, prulifloxacin seems to have a better safety profile.

No particular concern regarding serious hepatic or cardiac adverse events[5] was raised with any of the fluoroquinolones in the current study (<10 reports in 2005 and 2006) even though the

Table II. Most frequent adverse drug reactions (ADRs), classified by System Organ Classes (SOC) from the Medical Dictionary for Regulatory Activities, for each fluoroquinolone (numbers refer to the total for both years under study; SOCs with at least ten observations for one fluoroquinolone are shown)

SOC	Levofloxacin (n = 231)	Moxifloxacin (n = 118)	Ciprofloxacin (n = 110)	Prulifloxacin (n = 43)
	T/S (%)[a]	T/S (%)[a]	T/S (%)[a]	T/S (%)[a]
Skin	58/40 (25.1)	29/17 (24.6)	51/34 (46.4)	12/6 (27.9)
Musculoskeletal	57/19 (24.6)	3/1 (2.5)	12/5 (10.9)	4/1 (9.3)
Respiratory	24/17 (10.4)	8/6 (6.8)	1/1 (0.9)	7/1 (16.3)
Body as a whole	24/16 (10.4)	21/17 (17.8)	6/5 (5.5)	5/3 (11.6)
Nervous system	15/11 (6.5)	14/7 (11.9)	2/0 (1.8)	4/3 (9.3)
Cardiovascular	10/9 (4.3)	5/3 (4.2)	4/4 (3.6)	3/0 (7.0)
Psychiatric	8/6 (3.5)	12/3 (10.1)	7/3 (6.4)	6/3 (14.0)
Gastrointestinal	8/1 (3.5)	10/7 (8.5)	1/0 (0.9)	1/1 (2.3)
Genitourinary	8/8 (3.4)	4/4 (3.4)	7/6 (6.4)	

a % refers to the total number of ADRs for each fluoroquinolone.

T = total; **S** = serious.

Table III. Most frequent adverse drug reactions (ADRs), classified by preferred terms (PTs) from the Medical Dictionary for Regulatory Activities, for each fluoroquinolone under study (PTs are grouped according to their clinical meaning; PTs with at least ten observations within the database are shown)

Fluoroquinolone	Rash exanthema, erythema, urticaria (n = 93)	Anaphylactic shock (n = 14)	Dyspnoea (n = 13)	Achilles tendonitis, Achilles tendon rupture (n = 32)	Other tendonitis, tendon rupture (n = 14)
	T/S (%)[a]	T/S (%)[a]	T/S (%)[a]	T/S (%)[a]	T/S (%)[a]
Ciprofloxacin	31/17 (33.3)	1/1 (7.1)		5/0 (15.6)	3/3 (21.4)
Levofloxacin	30/16 (32.3)	5/5 (35.7)	9/5 (69.2)	24/7 (75.0)	10/2 (71.4)
Moxifloxacin	19/7 (20.4)	8/8 (57.1)	2/1 (15.4)	2/1 (6.3)	1/0 (7.1)
Prulifloxacin	9/4 (9.7)		2/2 (15.4)	1/1 (3.1)	
Ofloxacin	4/4 (4.3)				

a % refers to the total number of ADRs for each group of PTs.

T = total; **S** = serious.

spontaneous reporting system is considered a powerful tool for detecting very rare events. The underreporting phenomenon and/or the narrow time window (2 years) might contribute to explain this finding.

In conclusion, these results suggest the opportunity of a more appropriate choice among different fluoroquinolones when used in clinical practice based on their individual safety profiles. Indeed, most fluoroquinolones are indicated in the treatment of clinically relevant infectious diseases such as community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and uncomplicated and complicated urinary tract infections.[6,12] However, a study with a formal aetiological design (e.g. nested case-control or case-crossover study) should be conducted to confirm these findings, therefore overcoming the limitations due to ADR reporting.[33]

Limitations

This study has some limitations. First, these data are limited to extra-hospital (community) prescriptions of fluoroquinolones; this aspect could underestimate the denominator that was used to compute report or ADR/drug consumption ratios. However, we know that the largest volume of antibacterial agents is prescribed in primary care.[34-39]

Second, these findings are based on spontaneous reporting data. As a confirmation, the majority of cases reported here were 'possible' in terms of causality assessment. This means that, even though methodological literature[15,40] has reinforced the credibility of comparisons among molecules with similar indications through pharmacovigilance databases, an *ad hoc* pharmacoepidemiology study remains pivotal to substantiate these results,[15] so influencing the clinical decision-making process.

Third, the use of administrative databases cannot guarantee homogeneous data collection at a regional level.

Finally, although the regions involved in the survey are the most representative in terms of inhabitants and ADR reports, this does not allow a complete generalization of our findings to the entire Italian population.

Conclusions

The present survey constitutes the first analysis of fluoroquinolone safety profiles, including prulifloxacin. This antibacterial was found to be associated with more adverse effects than other fluoroquinolones in 2005 but with fewer ADRs in 2006, when its consumption increased. Greater usage data with prulifloxacin is probably required to determine its exact safety profile compared with other more commonly used fluoroquinolones. In the light of numerous limitations associated with pharmacovigilance data, further epidemiological studies are needed to confirm the present results and to extend these conclusions to a larger population.

Acknowledgements

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