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Profiles of Hepatic and Dysrhythmic Cardiovascular Events Following Use of Fluoroquinolone Antibacterials

Experience from Large Cohorts from the Drug Safety Research Unit Prescription-Event Monitoring Database

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Abstract

Objective: To investigate how frequently serious dysrhythmic cardiovascular, and hepatotoxic events are reported during routine clinical use of fluoroquinolones (quinolones) in general practice.

Design: Cohorts prescribed quinolones (cohort sizes: ciprofloxacin 11 477; enoxacin 2790; ofloxacin 11 033 and norfloxacin 11 110; mean age in each cohort of 48.6 to 57.0 years) were selected from the Drug Safety Research Unit's Prescription-Event Monitoring (PEM) database. The monitoring periods were November 1988 to January 1989 for ciprofloxacin; April 1989 to January 1991 for enoxacin; May 1991 to December 1991 for ofloxacin and October 1990 to October 1991 for norfloxacin. Data collected over the total PEM surveillance period on selected gastrointestinal events were extracted and reviewed to identify possible hepatic events, together with selected cardiovascular events associated with dysrhythmias. For each quinolone, times to onset of the event and patient-months of observation (denominator values) were calculated. The analysis was based on two observation periods: rate of event during the first 7 days following dispensing of a prescription for each drug (W_1), and rate of event during the second to sixth week inclusive (W_2).

Results: Scrutiny of original green forms revealed no evidence of drug-induced hepatic dysfunction within 42 days of drug administration for any of the quinolones monitored. No evidence was found of drug-induced dysrhythmic events associated with enoxacin within 42 days of drug administration. Of the other quinolones, 'atrial fibrillation' was reported most often within 42 days following ciprofloxacin administration, with no change in event rate over that time, crude relative risk (CRR)[W_1/W_2] 1.0 [95% confidence interval (CI) 0.02 to 8.92]. Other less serious events associated with dysrhythmia were reported with varying incidence within 42 days of quinolone administration. The crude rate of palpitation did not change significantly over that time for ciprofloxacin, ofloxacin and

norfloxacin: CRR 0.83 (95% CI 0.02 to 6.86), 2.00 (95% CI 0.19 to 12.20) and 4.99 (95% CI 0.06 to 391.94), respectively. Syncope and tachycardia were also reported for ofloxacin [CRR 9.99 (95% CI 0.52 to 589.49 for both events)] and ciprofloxacin [1.0 (95% CI 0.02, 8.92)] and 2.50 (95% CI 0.04, 47.96) for syncope and tachycardia, respectively].

Conclusion: It cannot be ruled out that some rare hepatic and dysrhythmic events associated with quinolones may be drug related. The primary purpose of PEM is signal generation. Compared with the other quinolones, ciprofloxacin was associated with the highest number of reports of dysrhythmic cardiovascular events occurring within 42 days of administration. This requires further investigation by other types of epidemiological study.

Fluoroquinolones have been in clinical use for up to 30 years, and have been found to be generally well tolerated. Post-marketing surveillance has identified severe adverse events, including QT prolongation and potential cardiotoxicity associated with the third- and fourth-generation quinolone agents, such as temafloxacin and grapafloxacin,[1] plus liver toxicity associated with trovafloxacin.[2] While it is clear that serious cardiovascular events have been recorded for these newer agents, it has been suggested that the phenomenon may be a class effect involving dose-dependent interference with human ether-ago-go related gene (HERG)-mediated potassium channel currents in the myocardium.[3] This may be potentiated by coadministration of other drugs known to prolong the QT interval.[4,5] However, this potential is not equal for all quinolones, with the second-generation agents demonstrating low intrinsic potential to block potassium channels.[6]

Rare but serious hepatotoxocity has been reported in retrospect for second-generation fluoroquinolones.[7] Hepatitis, cholestasis and hepatic failure have been reported infrequently with norfloxacin,[8-11] ofloxacin[12-14] and ciprofloxacin.[15-17] Severe cases (some fatal) have been reported with ciprofloxacin.[18,19]

The Drug Safety Research Unit (DSRU) monitors the safety of newly marketed drugs during their immediate post-marketing period in England, using the observational cohort technique of Prescription-Event Monitoring (PEM).[20] As part of its monitoring programme, the DSRU has carried out individual PEM studies of four quinolone antibacterial agents: ciprofloxacin, enoxacin, ofloxacin and norfloxacin.

The aims of this study are to investigate retrospectively using PEM cohorts, how frequently potentially serious gastrointestinal events related to hepatotoxicity and cardiovascular events related to dysrhythmia were reported during routine clinical use of second-generation quinolone antibacterial agents in general practice shortly after launch onto the UK market. In addition, these selected events are re-evaluated for signals of possible adverse drug reactions.

Methods

PEM is used as a form of post-marketing surveillance and the DSRU database currently holds data on 78 drugs of different therapeutic classes with a median cohort size of 11 296 [interquartile range (IQR) 8916 to 13 604]. The methodology of PEM has been described in detail elsewhere.[20] In summary, patients are identified by means of dispensed National Health Service prescription data supplied in confidence by the Prescription Pricing Authority (PPA) in England. Simple questionnaires (green forms) are posted to the prescribing general practitioner (GP) approximately 6 months after the date of the first prescription for each patient. The green forms request information on demographic data and any event experienced by patients during treatment.

The definition of an 'event' is given as 'any new

diagnosis, any referral to a consultant, or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in clinical values or any other complaint which was considered of sufficient importance to enter in the patient's notes, since the day the drug was started'.

Reported events are coded onto a computer using the DSRU event dictionary, which is arranged in system-organ classification with specific 'lower' terms grouped together under broader 'higher' terms. In addition, if the treatment was stopped the reason for stopping the drug, the date of stopping and any events reported after the medication was stopped are requested.

Each cohort consists of those patients for whom a green form questionnaire is returned containing useful clinical data. Those questionnaires returned with no information (clinical or other) provided are excluded, as there is no means of determining whether forms not completed indicated no reported events. In addition, patients no longer registered with a practice are not considered further.

Hepatic and Cardiovascular Events

For this study, those 'lower' terms indicating possible gastrointestinal events related to hepatotoxicity and cardiovascular system events possibly related to dysrhythmia were reviewed for each of the four quinolone antibacterials. Events that were unlikely to involve the liver, such as 'gastroenteritis', were excluded. Some common cardiovascular conditions, such as 'hypertension' and 'oedema' were excluded from the search, because they are frequent in older age groups, whether or not the individuals are receiving quinolone antibacterials. In order to identify any additional relevant hepatic or dysrhythmic cardiovascular events, cases reported with nonspecific event terms such as 'gastrointestinal unspecified' and 'cardiovascular unspecified' were individually assessed by scrutiny of the original green forms.

Deaths

In PEM, deaths with no specified cause were routinely followed up by requesting death certificates from the Office for National Statistics (ONS). If a death was considered to be 'possibly' related to the drug of interest, the general practice records were requested from the local Health Authority, after first gaining permission from the GP. Historically for some drugs, systematic requests for medical notes were not in place, such that for a minority of cases for the quinolones cause of death information is not available.

For this study where possible, the lifetime medical records and death certificates were scrutinised for patients who died within 30 days of commencing treatment with the quinolone antibacterials. These were used to ascertain whether the cause of death may have been attributed to the quinolone antibacterial treatment.

Analysis

Summary statistics of the demographic characteristics of the four quinolone cohorts were calculated; differences between categorical variables were tested using Pearson Chi-squared test, and differences between continuous variables tested by using parametric two sample t-tests, where appropriate.

The time to onset of the event for the total surveillance period was calculated for each fluoroquinolone, and the data were reviewed for evidence of temporal patterns. Generally adverse reactions for quinolones have been reported to occur in the first 7 to 10 days of therapy.[21,22] Nevertheless a small number of events, including idiosyncratic reactions (with the exception of immediate hypersensitivity reactions such as anaphylaxis) may take a considerable time to manifest, so that some events occurring after treatment may be delayed in their onset. Crude event rates during the first week of observation (W_1) and the second to sixth weeks of observation (W_2) were calculated for each selected event for each quinolone, irrespective of whether or not treatment was continued.

Comparison of these two periods (W_1/W_2) was tested to determine whether the rate of events changed over time.

In this study the word 'possibly' in relation to association of an event with drug treatment is used to indicate that because of the temporal relationship with drug administration a causal relationship cannot be ruled out. For the purposes of this study, the indication was taken to be constant whilst receiving treatment and individuals classed as 'first-time' users. Missing values were accounted for in the analysis by the exclusion of subjects with missing values for each individual variable under investigation.

Results

Data accrual was between November 1988 and December 1991. Table I and table II list the events of interest.

The proportions of questionnaires that were returned with clinically useful information ranged from 37.9 to 55.5% (table III).

Table I. Lower-term gastrointestinal events associated with hepatotoxicity. All reported events are coded into a database using a hierarchical dictionary arranged in a system organ classification with specific 'lower' terms grouped together under broader 'higher' terms

Bilirubinuria
Cirrhosis
Gastritis[a]
Gastrointestinal unspecified[a,b]
Hepatic failure[a]
Hepatitis[a]
Hepatomegaly
Hospital referrals: gastroenterology[a]
Jaundice cholestatic
Jaundice (nonspecified)[a]
Jaundice obstructive
Liver function test abnormal[a]
Laboratory test abnormal[a]
Liver transplantation
Nonmalignant tumour (liver)

a Events where original green forms were scrutinised to obtain further details.

b Unspecified = not coded elsewhere.

Table II. Lower-term cardiovascular events associated with dysrhythmia. All reported events are coded into a database by using a dictionary arranged in a system organ classification with specific 'lower' terms grouped together under broader 'higher' terms

Arrhythmia[a]
Atrial fibrillation[a]
Bradycardia
Cardiac arrest[a]
Cardiomyopathy
Cardiovascular system unspecified[a]
Extrasystoles
Faintness[a]
Heart block[a]
Hospital referrals: cardiology[a]
Ischaemic heart disease
Lost consciousness[a]
Myocardial infarction
Myocardial fibrosis
Palpitation[a]
Pain chest[a]
Tachycardia
Ventricular fibrillation

a Events where original green form questionnaires were scrutinised to obtain further detail on specified arrhythmias or on nonspecific terms which may have been associated with cardiac arrhythmias.

The summary characteristics of the PEM cohorts for the four quinolone antibacterials are shown in table III. The cohorts were predominantly female and the age distribution differed between the drug cohorts in women only but not in men [Kruskal-Wallis, df (3), $p < 0.0001$ and $p = 0.0454$, respectively].

The main indications reported for prescribing each quinolone are shown in table IV. Overall, the most common reason for prescribing ciprofloxacin and ofloxacin was for lower respiratory tract infection. In contrast, for enoxacin and norfloxacin the most common indication was urinary tract infection. Such variations are to be expected given the difference in marketing authorisation for each drug.

With anti-infective agents many adverse reactions tend to occur early, commonly during the first week after the initial prescription, or shortly after. Tables V and VI present separately the number of lower-term potentially hepatotoxic gastrointestinal

events (table V) and cardiovascular events possibly related to dysrhythmia (table VI) reported during the first week (W_1), the second to sixth week combined (W_2), and the total PEM study observation period.

A total of 310 (0.85%) patients were identified as having experienced one or more gastrointestinal events of interest during the observation period. The median (IQR) duration of treatment in days for this subgroup was 7 (IQR 7 to 20) for ciprofloxacin; 4.5 for enoxacin (3 to 6); 6 for ofloxacin (6 to 7); and 3 for norfloxacin (3 to 8). Of these, 33 patients had 34 events reported on green form questionnaires, which were considered possibly associated with hepatotoxicity during the observation period (table V). The most commonly reported hepatotoxic event was 'jaundice unspecified' [20.6% (7/34)] and 'abnormal liver function test' [23.5% (8/34)]; the highest number of events were reported for ciprofloxacin [44.1% (14/34)], followed by ofloxacin [35.3% (12/34)]. No fatalities were reported, nor were any of these events given as a reason for stopping the antibacterial in any of these cohorts. The median age for this subset was 64 years (IQR 19 to 89); 19 men and 14 women.

Out of 752 cardiac events reviewed, 280 events possibly associated with dysrhythmia were reported on green form questionnaires for 269 patients during the total observation period (table VI). The median age was 67 (IQR 17 to 91), with 92 (32.9%) men and 184 (65.7%) women. The median (IQR) duration of treatment in days for this subgroup was: 7 (IQR 7 to 7) for ciprofloxacin; 3 (3 to 5) for enoxacin; 5 (5 to 7) for ofloxacin; and 3 (3 to 7) for norfloxacin.

The most commonly reported events were 'syncope' [27.9% (78/280)], 'palpitations' [27.1% (76/280)], 'atrial fibrillation' [20.7% (58/280)] and 'tachycardia' [7.9% (22/280)]. The highest numbers of events were reported for patients treated with ciprofloxacin. There were no clear difference in the types of events reported (Fishers Exact test, $p = 0.510$). Ofloxacin and ciprofloxacin had the highest number of reports for serious events such

Table III. Summary characteristics of fluoroquinolone Prescription-Event Monitoring (PEM) cohorts

Quinolone	Ciprofloxacin	Enoxacin	Ofloxacin	Norfloxacin
PEM study period	Nov 1988-Jan 1989	Apr 1989-Jan 1991	May 1991-Dec 1991	Oct 1990-Oct 1991
Response rate (%)	55.5	37.9	39.7	42.7
Size of cohort	11477	2790	11033	11110
Total cohort				
Median age in years (IQR) [a]	57 (37 to 71)	47 (32 to 66)	54 (35 to 69)	48 (31 to 67)
Age not specified: n (%)	1676 (14.6)	335 (12.0)	1417 (12.8)	1128 (10.2)
Gender not specified: n (%)	372 (3.3)	39 (1.4)	141 (1.3)	160 (1.4)
Men				
Number (%) [b]	4493 (39.1)	475 (17.0)	4263 (38.6)	1852 (16.7)
Median age in years (IQR)	59 (41 to 72)	58 (43 to 73)	59 (42 to 70)	61 (43 to 72)
Women				
Number (%)[b]	6612 (57.6)	2276 (81.6)	6629 (60.1)	9098 (81.9)
Median age in years (IQR)	55 (36 to 71)	45 (30 to 64)	50 (3 to 67)	46 (30 to 65)
Patient-weeks of observation[c]				
Week 1 (1 to 7 days)	11477	2790	11033	11110
Weeks 2 to 6 (8 to 42 days)	57314	13874	55112	55481
Total	**333210**	**177437**	**756470**	**333210**

a Comparison of age (years) between drug cohorts: Kruskal-Wallis, df(3), $p < 0.0001$.

b Comparison of gender distribution, chi-squared test, df(3), $p < 0.0001$.

c Numbers diminish slightly during period of observation due to patients lost to surveillance.

IQR = interquartile range.

Table IV. Common indications for prescribing each quinolone

Indication	Ciprofloxacin		Enoxacin		Ofloxacin		Norfloxacin	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Lower respiratory chest infection	4197	36.6	17	0.6	5202	47.1	9	0.1
Urinary tract infection	2031	17.7	2102	75.3	1251	11.3	8936	80.4
Upper respiratory tract infection	1169	10.2	10	0.4	989	9.0	7	0.1
Infection skin[a]	839	7.3	16	0.6	296	2.7	5	<0.1
Chronic obstructive airways disease	179	1.6	1	<0.1	253	2.3	0	
Pelvic inflammatory disease	138	1.2	4	0.1	451	4.1	1	<0.1
Micturition disorder[b]	31	0.3	155	5.6	55	0.5	705	6.3
Other indications	2111	18.4	76	2.7	1274	11.5	198	1.8
Indication not specified	782	6.8	409	14.7	1262	11.4	1249	11.2
Total	**11477**	**100.0**	**2790**	**100.0**	**11033**	**100.0**	**11110**	**100.0**

a Infection skin includes unspecified and local bacterial (including cellulitis).

b Micturition disorder includes dysuria which may also involve urinary tract infection.

as atrial fibrillation with one report of ventricular fibrillation. Events were classified as 'serious' using the International Conference on Harmonisation (ICH) definitions[23] where a serious reported event is defined 'as any untoward medical occurrence that at any dose that: results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect'. In contrast, norfloxacin had a high proportion of nonspecific events 'palpitations' and 'syncope', which are descriptions of symptoms which could be associated with many cardiac effects. Enoxacin had the lowest number of reports for serious and nonserious dysrhythmic events.

Figures 1(a) and (b) show the number of selected hepatic and dysrhythmic events (all types) for the first 6 months of the observation period for each quinolone. There was no difference in the time to onset of reported hepatotoxic events between the four quinolones [Kruskal-Wallis test, df (3), p = 0.1194], although for ciprofloxacin the majority of hepatotoxic events occurred within the first 5 months [median 126 days (IQR 62 to 147)]. For ofloxacin, the time to hep-

Table V. Number of hepatotoxic-related gastrointestinal events for four quinolone drugs for observation week 1, weeks 2 to 6 inclusive, and the total Prescription-Event Monitoring observational period

Hepatoxic event	Ciprofloxacin			Enoxoxacin			Ofloxacin			Norfloxacin			All
	wk 1	wks 2-6	total	wk 1	wks 2-6	total	wk 1	wks 2-6	total	wk 1	wks 2-6	total	total
Bilirubinuria			1										1
Cirrhosis							1		1				1
Gastrointestinal unspecified		1	1										1
Hepatic failure			2						2				4
Hepatitis			1						1			2	4
Hepatomegaly			3						1				4
Hospital referrals: gastroenterology											1	1	1
Jaundice (unspecified)			4			1			2				7
Jaundice cholestatic												1	1
Jaundice obstructive									1				1
Laboratory test abnormal		1	1										1
Liver function test abnormal			2			1			4			1	8
Total		**2**	**15**			**2**	**1**		**12**		**1**	**5**	**34**

Table VI. Number of dysrhythmic cardiovascular events for four quinolone drugs for observation week 1, weeks 2 to 6 inclusive, and the total Prescription-Event Monitoring observational period

Cardiovascular event	Ciprofloxacin			Enoxacin			Ofloxacin			Norfloxacin			All
	wk 1	wks 2-6	total	wk 1	wks 2-6	total	wk 1	wks 2-6	total	wk 1	wks 2-6	total	total
Arhythmia		2	4		1	1			2			3	10
Atrial fibrillation	1	5	17		1	7		1	20		1	14	58
Bradycardia												1	1
Extrasystoles			4			2			3		1	1	10
Lost consciousness						1							1
Pain chest		2	10		1	3			5			2	20
Palpitation	1	6	26			7	2	5	18	1	1	25	76
Sick-sinus syndrome			1						1			1	3
Syncope	1	5	21	1		5	2	1	24	1	1	28	78
Tachycardia	1	2	7		1	1	2	1	8		1	6	22
Ventricular fibrillation			1										1
Total	**4**	**22**	**91**	**1**	**4**	**27**	**6**	**8**	**81**	**2**	**5**	**81**	**280**

atotoxic event was much longer [median 347 days (IQR 185.5 to 376)]. For norfloxacin and enoxacin the number of hepatotoxicity reports was small, the time to event reported for the one event for enoxacin was 357 days, and for four events for norfloxacin the median was 276 days (IQR 4.5 to 440.5).

Conversely there was a significant difference in time to onset of reported dysrhythmic events between the quinolones [Kruskal-Wallis, df (3), $p < 0.0001$]. There were a higher number of potentially dysrhythmic cardiovascular events reported with ciprofloxacin during the first 6 weeks and the overall observation period compared with other quinolones. The median time to onset of reported events for ciprofloxacin was 67.5 days (IQR 30 to 127) compared with enoxacin [median 147 days (IQR 53 to 262)], ofloxacin [median 180 (IQR 64 to 314)] and norfloxacin [median 190 days (IQR 85 to 325)]. A summary of the 'time to event' distribution is presented in figure 1. The crude rate per 1000 patient-weeks of observation for dysrhythmic cardiovascular events for each quinolone is shown in figure 2.

It is unlikely that reports occurring more than 6 weeks after the start of treatment with quinolone antibacterials are causally associated with the drugs. It is clear that the number of hepatotoxic reports is very low and a comparison between quinolones is not feasible. However, the crude relative risk (W_1/W_2) for individual dysrhythmic events where the number of events in the first week was equal to or greater than 1.0, are presented in table VII.

It has been postulated that where the relative risk is greater than or equal to 3.0, the events are likely to be either a result of a reaction to a drug, or a sign or symptom of the disorder being treated.[24] This value suggests that the event occurs more frequently during the treatment week than in the subsequent weeks. From table VII it can be seen that the crude unadjusted relative risk exceeds the value of 3 for the events 'syncope' and 'tachycardia' in patients treated with ofloxacin; and events 'palpitations' and 'syncope' for patients treated with norfloxacin. However, because of the small numbers involved the precision of these estimates is poor. This is reflected by the wide 95% confidence intervals accompanied by a lack of statistical significance.

Deaths

Numbers of deaths that occurred within 30 days of quinolone antibacterial treatment are shown in table VIII. From the information available, none of the deaths was considered directly attributable to the quinolone treatment.

Discussion

The main aim of this study was to determine whether there was any evidence in the DSRU data-

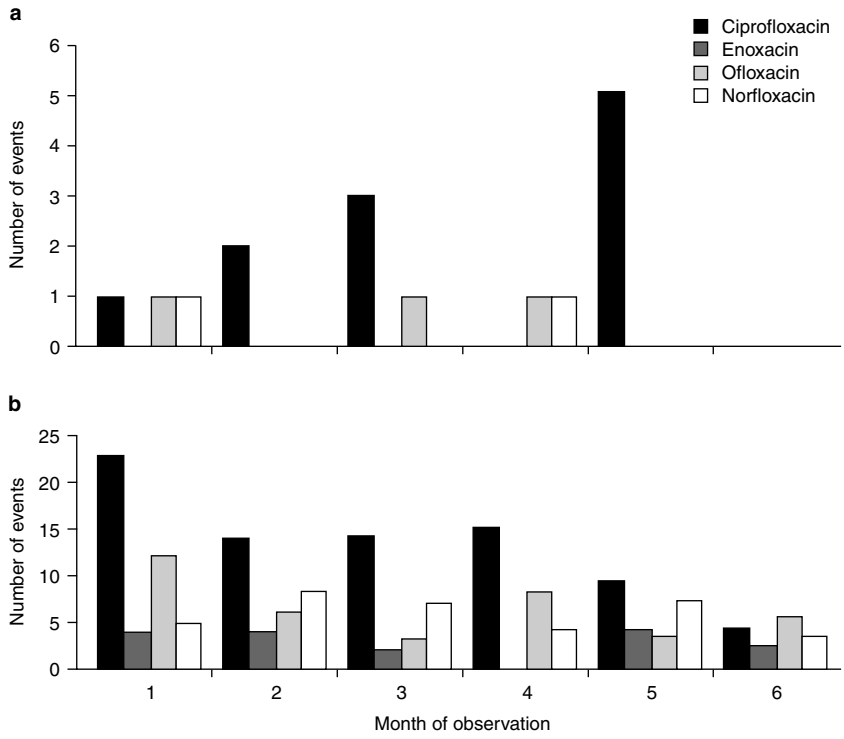

Fig. 1. (**a**) Number of events (all types) possibly related to hepatotoxicity for the first 6 months of observation for each quinolone. (**b**) Number of cardiovascular events (all types) possibly associated with dysrhythmia for the first 6 months observation period for each quinolone.

base to support the view that quinolone use may be associated with serious hepatic disorders[7,15,25] or uncommon cardiovascular dysrhythmias such as the potentially lethal paroxysmal ventricular arrhythmia known as torsade de pointes.[4,5]

This study was a retrospective review of systematically collected event data from general population-based cohorts of users of four quinolone antibacterial drugs held in the DRSU PEM database. The methodology incorporated re-assessment of the green form questionnaires returned by GPs, and calculation of crude event rates per 1000 patient weeks of observation during and shortly after treatment.

According to Bradford-Hill's criteria,[26] events are more likely to be drug related when they occur within a plausible temporal relationship to drug administration. This is possibly of greater importance when, as is frequently the case with quinolone antibacterials, the drug is used only for a short period of time. In this study, we compared the first week of observation to the second to sixth week inclusive of observation. A more sensitive analysis would have been to compare the ratio of person-time at risk to an event during treatment, to that after treatment. Since the median duration of treatment reported for these four drugs was for 1 week or less, the comparison with weeks 2 to 6 inclusive was felt to be appropriate estimate of the 'off-treatment' period. We did not know whether patients who stopped treatment then continued with another drug.

Pre-marketing clinical trials for ciprofloxacin include reports of cholestatic jaundice of mild to moderate severity.[27] Similar trials for ofloxacin, enoxacin and norfloxacin also indicated elevated

hepatic laboratory indices, but no serious hepatotoxic events.[27] Conversely, post-marketing studies on these drugs report serious hepatotoxic events such as hepatic necrosis, jaundice, pancreatitis and elevation of hepatic laboratory parameters, with an incidence of less than 1%.[28] Similarly, dysrhythmic cardiovascular events reported from pre-marketing clinical investigations for ciprofloxacin include 'palpitation', 'atrial flutter', 'dysrhythmia', 'ventricular ectopy', and 'syncope' at an incidence of less than 1% in 2799 patients,[27] although serious events tended to be related to IV administration. Similar data for ofloxacin, enoxacin and norfloxacin include 'tachycardia', 'palpitations', 'syncope' and 'chest pain' at an incidence of between 0.1 and 1%.[27]

The incidence risk of all hepatotoxic events, for all four quinolones in this study was reported to be less than 0.1% (33/ 36410 patients). Unfortunately there were insufficient data to link use of quinolone antibacterials to drug-induced hepatic disorders, or to calculate and compare incidence rate individually for each quinolone for the two time periods of interest. The majority of events were reported to have occurred off treatment after the second month, and ciprofloxacin accounted for 44% of reports.

It was noted that there were several reports where liver function tests were reported as abnormal, as well as several reported cases of jaundice (all types) after 42 days from starting treatment

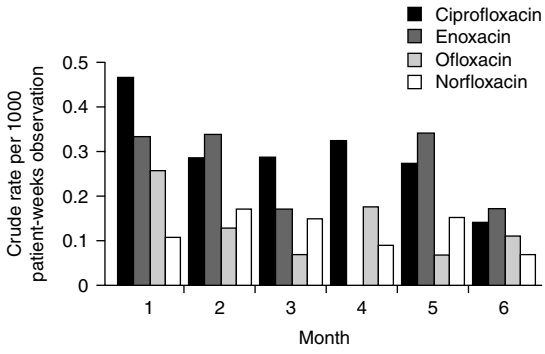

Fig. 2. Crude rate of dysrhythmic events (all types) per 1000 patient weeks of observation for the first 6 months observation period for each quinolone.

(table V). Some drug-induced serious events such as cirrhosis or hepatic failure may be insidious in their development and thus abnormalities in liver function tests may not be looked for, or detected, for some time following drug administration. Some events reported in these studies may have been long latency events of this type, but it was not possible in a historical cohort study of this type to ascribe causality. However, it is likely that most events reported late in the observation periods represent background events. Because the studies were conducted more than 10 years ago, it is unlikely that requests for additional information to enable assessment of the association of the event to the use of the drug would have been successful.

There was also insufficient evidence from this study to support or reject the possibility that use of quinolone antibacterials is associated with serious dysrhythmias, such torsade de pointes, with an estimated incidence of between 1 per 12 000 to 1 per 120 000 patients.[29] Further epidemiological studies are needed to test this hypothesis. Other serious and nonserious dysrhythmic events were reported (table VI) and there are differences in the event profiles between the quinolones. There were six cases of atrial fibrillation reported for ciprofloxacin within 42 days after starting treatment, but the crude event rate did not change over time [relative risk 1.0 (95% CI 0.02 to 8.92)]. Various nonspecific descriptive events were reported in the first week, but these differed between the four quinolones. Although the magnitude of relative risk comparing the two time periods was high for the events 'palpitations' and 'syncope' reported for ofloxacin and norfloxacin, the wide confidence interval reflects the lack of precision of the estimates (table VII).

The strengths and limitations of PEM have been described elsewhere.[30] PEM uses event data, which are subject to a variety of biases that could influence these observations. The number of patients prescribed enoxacin was less than with the other three drugs. Ciprofloxacin was monitored for a shorter period than the other quinolones (table III), but the periods over which these studies were

carried out on the other three drugs were of similar duration. Another possible source of bias is the order in which the drugs entered the UK market. Ciprofloxacin and enoxacin were marketed earlier than ofloxacin and norfloxacin and consequently monitoring was carried out earlier. However, studies between the first and latest drug in other therapeutic groups using PEM cohorts demonstrates that incidence of events is reasonably constant arguing against differential reporting affecting event reporting rates[31] in PEM studies. Furthermore, although at the DSRU monitoring of the quinolone antibacterials was carried out 10 to 12 years ago, the age of the data is not considered to contribute any significant bias. GPs were, as now, asked to report all events whether or not these were considered causally related to the drug being monitored.

Age and gender are known to effect the reporting of adverse events[32] and have been shown to differ between the quinolone cohorts examined in this study. The enoxacin, norfloxacin and ofloxacin cohorts were significantly younger (table III) than the ciprofloxacin cohort. These differences could reflect that ciprofloxacin is prescribed for more severe illness than the other quinolones. Because two of the quinolones, enoxacin and norfloxacin, are used mainly for treatment of urinary tract infections, the percentage of women in the cohorts (81.6% and 81.9%, respectively) prescribed these drugs was significantly higher than for ciprofloxacin and ofloxacin (57.6% and 60.1%, respectively) [table III]. Where the indications are similar (ciprofloxacin versus ofloxacin and enoxacin versus norfloxacin), the proportion of women did not differ significantly. Because of the small numbers reported with each event, comparisons of relative risk adjusted for the potential confounders of age and gender were not possible, although we acknowledge that for comparative purposes adjusted rate ratios are more appropriate.

The difference in indication is probably the most important cause of possible bias influencing these results. The different indications emphasised in the marketing literature for the different quinolones is reflected in the main reasons given for prescribing each drug in this study (table IV). Ciprofloxacin and ofloxacin are indicated for treatment of severe infections, especially where extensive tissue penetration is needed. As well as lower respiratory tract infections, these include severe systemic infections such as cellulitis and infections in immunosuppressed patients. However, this does not invalidate the observation that use of these two quinolones may be associated with a significantly higher incidence of hepatic and cardiovascular system events compared with the other quinolones. Because enoxacin and norfloxacin have been marketed mainly for the treatment of urinary tract infection (prescribers' information leaflets) they are used mainly in less seriously ill and, as reflected by the

Table VII. Event rates for each quinolone[a] per 1000 patient-weeks and relative risk (W_1/W_2) when one or more events were reported occur within the first week

Event	Rate W_1	Rate W_2	Rate ratio (W_1/W_2)	95% Confidence interval	p Value
Ciprofloxacin					
Atrial fibrillation	0.087	0.087	0.999	0.021, 8.925	1.000
Palpitation	0.087	0.105	0.832	0.018, 6.861	0.948
Syncope	0.087	0.087	0.999	0.021, 8.925	1.000
Tachycardia	0.087	0.035	2.497	0.042, 4.097	0.496
Ofloxacin					
Palpitation	0.181	0.091	2.000	0190, 12.204	0.427
Syncope	0.181	0.018	9.990	0.520, 589.494	0.079
Tachycardia	0.181	0.018	9.990	0.520, 589.494	0.079
Norfloxacin					
Palpitation	0.090	0.018	4.994	0.064, 391.941	0.334
Syncope	0.090	0.018	4.994	0.064, 391.941	0.334

a Enoxacin is not included because no events were reported during the period.

Table VIII. Deaths within 30 days of starting quinolone treatment

Drug	Total number of deaths in cohort	Days to event 1 to 8	Days to event 9 to 15	Days to event 16 to 22	Days to event 23 to 30	Total number within 30 days
Ciprofloxacin	536	45	15	26	19	105
Enoxoxacin	120	0	0	2	2	4
Ofloxacin	793	14	13	7	7	41
Norfloxacin	445	4	9	8	3	24

age differences reported in this study, in younger predominantly female, patients. This may help explain the comparatively low rate of dysrhythmic events associated with these drugs.

Finally, it is not possible to exclude confounders such as past medical history, concurrent illness and medication. Information on these variables recorded on the green forms is often incomplete. Such detail is essential for definitive causality assessment; prescribing information recommends care when co-prescribing drugs metabolised primarily through the liver, as well as dose reduction in patients with impaired renal function.

Conclusions

The incidence of uncommon adverse events reported in publications from preclinical trials should be interpreted with caution as they are often based on small numbers, and only apply to patients meeting specific study inclusion and exclusion criteria. There are clear differences in the ability of pre- and post-marketing studies to detect uncommon events, including differences in intensity of event recording and reporting. In addition, reviews of published preclinical studies rarely provide details of the time to event and this means that treatment emergent events cannot accurately be defined. Our study contributes an estimate of the incidence rate of these events during and shortly after treatment, which is important when trying to establish the temporal relationship of drug exposure and event. Pharmacoepidemiological studies using systematically collected data such as PEM can be used to identify and calculate the incidence of adverse events, with an increased ability to identify rare adverse drug reactions compared with randomised, controlled trials. However, very rare events with an incidence of less than 1 : 3333 will either not be detected by PEM in the immediate postmarketing period in the first 10 000 patients, or will only be encountered by chance.[33]

The completeness of the information needs to be considered when evaluating results from observational studies such as PEM studies. This depends not only on the events occurring, but also on the patient reporting the event to the physician and the physician recording the events. While reporting rates in PEM are higher than those in spontaneous reporting schemes,[34] under reporting does occur.

Although, overall, the DSRU data indicate that hepatic and serious cardiovascular system events are rare, the different event profiles suggest that some hepatic and dysrhythmic events are more common following use of certain second generation quinolones, namely ciprofloxacin and ofloxacin, compared with the other quinolones in that class.

Some rare hepatic and dysrhythmic events may be drug related, but additional information to address possible confounding factors and bias is needed to ascribe a causal relationship. The primary purpose of PEM is signal generation with a secondary outcome of estimating incidence rate and risk of such events in normal clinical practice. Our study has highlighted possible signals that relate some dysrhythmic events to use of the second generation quinolones, ciprofloxacin and ofloxacin. These signals require validation by other types of epidemiological studies.

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