A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies

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1 The safety in everyday clinical usage of three 4-quinolone antibiotics, (ciprofloxacin, norfloxacin and ofloxacin), was compared with similar data for azithromycin and cefixime, each agent being examined by Prescription-Event Monitoring (PEM) during the early post-marketing period.

2 In PEM the exposure data are derived from general practitioner prescriptions confidentially provided by the Prescription Pricing Authority. Outcome data are provided by questionnaires (green forms) on which the prescribing medical practitioner records event data. When necessary, further information is obtained from a number of sources which include follow-up of all pregnancies and the patients' life-time medical record.

3 The main outcome measures were demographic information, including the patient's date of birth and sex; the indication for prescribing the drug being monitored; the reason for stopping treatment; the start and stop dates of treatment and the events recorded during and after treatment.

4 The final cohort for each of the five antibiotics exceeded 11000 patients. The only event significantly related to the use of all five antibiotics was nausea/vomiting. This was also the most frequent adverse event causing treatment to be discontinued with norfloxacin, ofloxacin and azithromycin (relevant information was not requested in the studies of ciprofloxacin and cefixime). Vaginal candidiasis was significantly more frequently associated with the use of the three 4-quinolones than with azithromycin and cefixime but it was frequently delayed until the week or two after the cessation of therapy. Within each event, as recorded in these studies, the highest event rates (the number of events per 1000 patients) in the week following the start of therapy were: 9.2 for diarrhoea with cefixime; 4.9 for nausea/vomiting with ofloxacin; 2.4 for rash with azithromycin; 2.2 for abdominal pain with norfloxacin; 1.5 for headache/migraine with ofloxacin; 1.4 for malaise/lassitude with ofloxacin; 1.2 for dizziness with norfloxacin. Uncommon events (reported in less than 1 : 1000 patients) included rare cases of allergic phenomena, convulsions and pseudo-membranous colitis. There were no reports of tendinitis, tenosynovitis or tendon rupture in children but tendon disorders were reported in the two months following the start of treatment in 20 adults. A total of 307 pregnancies were reported. Thirty-eight of the 55 women who received these drugs during the first trimester of pregnancy gave birth to healthy babies. No congenital abnormalities were reported. Apart from one case of unconfirmed pseudo-membranous colitis, none of the other 2468 deaths that occurred in these studies was attributed to the antibiotics.

5 These five antibiotics are acceptably safe antimicrobial agents when used in general medical practice. PEM is an effective method for monitoring the safety of recently introduced antimicrobial agents.

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Introduction

The 4-quinolone antibacterial agents include acrosoxacin, ciprofloxacin, ofloxacin, and the urinary antiseptics, cinoxacin, nalidixic acid and norfloxacin. Antibiotics of this group have been associated with reports [1] of tendinitis and tendon rupture, although large studies quantifying the incidence of these reactions have not previously been available. It is advised that the 4-quinolones should be used with caution in children or adolescents as arthropathy has been reported in weight-bearing joints in young animals [2]. It is of interest, therefore, to compare the results of post-marketing surveillance studies of these drugs with the results of studies of antibiotics that are frequently used in young people (azithromycin and cefixime). Accordingly, this paper compares the results of five observational cohort studies which have examined the safety of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime. Each of these studies provided information on over 11000 patients and was conducted by Prescription-Event Monitoring (PEM) [3–5].

Method

In each of these studies the exposure data were derived from NHS prescriptions written by general practitioners and provided, in confidence, by the Prescription Pricing Authority (PPA) in England. The outcome data comprise event reports obtained by sending questionnaires (green forms) to the doctors who wrote the individual prescriptions. The interval between the date of the prescription and the sending of the green form was approximately 6 months in the studies of ciprofloxacin and cefixime and 12 months in the studies of norfloxacin, ofloxacin and azithromycin. The return section of the green forms was anonymized and asked for information on the patient's sex, date of birth, the indication for prescribing the drug being monitored, the reason for stopping it, its effectiveness, the start and stop dates of treatment with the drug, and events during and after therapy with the dates of these happenings. An event was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration or improvement in a concurrent illness, any suspected drug reaction, or any complaint which was considered of sufficient importance to enter in the patient's notes. Only one green form was sent for each patient and no doctor was sent more than four green forms in any one month.

Deaths were followed up, where appropriate, by obtaining the permission of the general practitioner and then retrieving the life-time medical record of the patient from the Family Health Service Authority (FHSA). When needed, copies of the death certificates were obtained from the Office of Population Censuses and Surveys (OPCS). Pregnancies and selected events were followed up by obtaining additional information from the patient's doctor.

The prescriptions examined were written during November 1988 to January 1989 for ciprofloxacin; October 1990 to October 1991 for norfloxacin; May 1990 to December 1991 for ofloxacin; March 1992 to June 1993 for azithromycin and September 1990 to May 1991 for cefixime.

In handling the event data the confidence intervals for the difference between the event rate in the week of the onset of therapy (W_1) and the mean event rate in the following 5 weeks (W_2) have been calculated using the Poisson model [6–8] as:

$$W_1 - W_2 \pm 1000 \times a \sqrt{\frac{N_1}{D_1^2} + \frac{N_2 + N_3 + N_4 + N_5 + N_6}{(D_2 + D_3 + D_4 + D_5 + D_6)^2}}$$

$$= W_1 - W_2 \pm 1000 \times a \sqrt{\frac{N_1}{D_1^2} + \frac{N_{2-6}}{(D_{2-6})^2}}$$

Where N_1, number of reports in week 1 from the onset of therapy; N_{2-6}, number of reports in the following 2nd to 6th weeks; D_1, number of patients in the cohort in the week of the commencement of therapy; D_{2-6}, number of patients in the cohort on the subsequent 2nd to 6th weeks and the value of $a = 2.58$ for the 99% confidence interval.

These studies were conducted in accordance with the 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (CIOMS/WHO, Geneva, 1993) [9].

Results

The number of green forms sent out, the size of the final cohorts and their age distribution and sex, are shown in Table 1.

Indications, dose, adverse reactions, effectiveness

Ciprofloxacin was used in 6108 patients with respiratory tract infections (53.2% of the cohort) and in 2060 (17.9%) subjects with urinary tract infections; 2527 (22.0%) of the 11 477 patients received the drug for a wide variety of infections and in the remaining 782 (6.8%) the indication was not reported. There were 43 children aged less than 10 years (0.4% of the cohort). A random sample of the first prescriptions for 1000 patients showed that 45.4% received 500 mg day^{-1},

Table 1 Size of the cohorts, age distribution and sex of the patients

	Ciprofloxacin	*Norfloxacin*	*Ofloxacin*	*Azithromycin*	*Cefixime*
Number of green forms sent out	20 664	26 036	27 787	23 900	35 526
Number returned	12 394	13 029	12 698	12 535	12 880
Number void*	917	1919	1665	1260	1630
Size of final cohort	11 477	11 110	11 033	11 275	11 250
Males					
Number	4494	1852	4264	4532	4799
(% of cohort)	(39%)	(17%)	(39%)	(40%)	(43%)
Mean age ± 1 s.d. (years)	55.5 ± 20.0	57.1 ± 19.0	55.6 ± 18.9	33.7 ± 27.9	36.8 ± 27.7
Females					
Number	6613	9100	6627	6575	6223
(% of cohort)	(58%)	(82%)	(60%)	(58%)	(55%)
Mean age ± 1 s.d. (years)	53.2 ± 20.9	48.0 ± 20.4	50.5 ± 20.0	37.9 ± 25.9	39.9 ± 26.2
Not known					
Sex	370	158	142	168	228
(% of cohort)	(3%)	(1%)	(1%)	(2%)	(2%)
Age	1491	955	1153	738	1039
(% of cohort)	(13%)	(9%)	(10%)	(7%)	(9%)

* Includes patients no longer registered with doctor, blank forms, no record of treatment in the notes, patient's doctor moved or retired or died, prescribed drug not taken

41.6% 1000 mg day^{-1} and the remainder a range of doses from 125 to 2000 mg day^{-1}. The prescribers reported 19 adverse reactions to the drug (rash 6, diarrhoea 3, photosensitivity 2 and abdominal distention, anorexia, eczema, flatulence, joint pain, malaise, vomiting and vulvitis—each reported once); 12 of these 19 ADRs had been reported to the CSM. Of the 10 877 reports which included an opinion about effectiveness, ciprofloxacin was said to have been effective in 9822 (90.3%).

Norfloxacin was overwhelmingly used for urinary tract infections (9733, 87.6%), almost always in a dose of 800 mg day^{-1} (from a 1000 patient sample). There were seven children aged less than 10 years (0.1% of the cohort). Thirteen ADRs were reported (rash 3, allergic reaction 2, and diarrhoea, dizziness, nausea, oedema, oedema of the face, pruritus, rhinitis and vomiting—each reported once); two of these 13 reactions had been reported to the CSM. 9142 (92.1%) of the 9924 reports which gave an opinion on the subject declared the drug to have been effective.

Ofloxacin was used in 6726 (61.0%) patients with respiratory tract infections, 1317 (11.9%) subjects with urinary tract infections and 1728 (15.7%) patients with a range of infections; the indication was not reported in the remaining 1262 (11.4%) of the cohort. There were 11 children aged less than 10 years (0.1% of the cohort). Over 75% of the patients in a 1000 patient sample received 400 mg day^{-1}. Twenty ADRs were reported (angioneurotic oedema, rash and vomiting—each reported twice and a range of reactions, each reported once); eight of these reactions had been reported to the CSM. Ofloxacin was reported effective in 8704 (89.9%) of the 9681 reports that gave an opinion on this subject.

Azithromycin was used in 7173 patients with respirat-

ory tract infections (63.6% of the cohort) and in 75 patients (0.7%) with urinary tract infections; 2778 (24.6%) of the 11275 patients received the drug for a wide variety of infections and in the remaining 1249 (11.1%) the indication was not reported. There were 2846 children aged less than 10 years old forming 25% of the cohort. These children were treated with azithromycin mainly for respiratory tract infections (55%) and ear infections (30%). In this study, information on the doses prescribed was not processed. Six events were reported as adverse reactions to azithromycin, (rash 2, dizziness, dyspnoea, oedema face and swollen tongue—each reported only once) three of which had been reported to the CSM. Azithromycin was said to have been effective in 9545 (92.4%) of the 10 329 reports which included an opinion about effectiveness.

Cefixime was used in 6962 patients with respiratory tract infections (61.9% of the total cohort) and in 494 (4.4%) of the patients with urinary tract infections; 2645 (23.5%) of the 11 250 patients were prescribed this drug for a wide variety of infections and in the remaining 1149 patients (10.2%) the indication was not specified. There were 2450 children aged less than 10 years old forming 22% of the cohort. These children were treated with cefixime mainly for respiratory tract infections (44%) and ear infections (43%). A random sample of the first prescriptions for 1000 patients showed that 70.2% were prescribed 200 mg day^{-1}, 14.4% 100 mg day^{-1}, 12.1% 400 mg day^{-1} and the remainder a range of doses from 75 mg day^{-1} to 800 mg day^{-1}. Six events were reported as adverse reactions to cefixime (pseudomembranous colitis—3, of which one was fatal, erythema multiforme, rash and urticaria—each reported once); three of these six ADRs had been reported to the CSM. Cefixime was said to have been effective in 9252 (91.4%)

of the 10 124 reports which included an opinion about effectiveness.

It is of interest that the number of events per 1000 days of treatment varied very little between the drugs (mean value 5.12, s.d. $\pm$ 0.42, range 4.45–5.50).

Experience from early PEM studies showed that it would be informative to ask the reason for stopping the monitored drug. Responses to this question were recorded in the norfloxacin, ofloxacin and azithromycin studies. The results are shown in Table 2 and indicate that gastro-intestinal adverse effects predominate as reasons for discontinuing therapy; allergic reactions also occur and are detected by this question.

The events recorded in 1 in 1000 patients, or more frequently, during the first week of therapy, compared with the subsequent 5 weeks in these five separate studies are summarized in Table 3. For each listed event this table shows the number of events in week 1 (N_1) and the event rate (W_1) per 1000 patients ($W_1 = N_1/D_1$ where D_1 is the number of patients exposed in the first week after the start of therapy). Table 3 also shows the number of events over the 5 weeks following therapy (N_2) and the mean event rate (W_2) over this same period.

Relatively high event rates for week 1 compared with subsequent weeks (Table 3) suggest early onset adverse effects [10] or that the event is a sign or symptom of the condition for which the drug is being given or that it is a feature of concomitant disease or concurrent medication or that it is a symptom which improved as a result of therapy.

Table 3 includes those events for which, for any one of the antibiotics examined, the event rate in week 1 is ≥ 1 in 1000 patients and the 99% confidence intervals are positive and do not include zero (that is, those events for which $W_1 - W_2$ is significant at the $P < 0.01$ level of confidence).

Events concerned with the respiratory and genito-urinary systems, (and hospital referrals), seem likely to be associated with the illnesses for which the anti-microbial agents were prescribed. Events possibly confounded by indication in this way have not been included in Table 3 but have been examined by scrutiny of the individual green form reports.

Events associated with therapy

The only event common to all five antibiotics (Table 3), and in which the event rate in the week following the commencement of therapy was significantly greater than the mean of that in the following 5 weeks, was nausea/vomiting. This was reported some 3 to 5 times per thousand patients in the week of commencement of therapy. Nausea/vomiting was also the most frequent adverse event causing treatment to be discontinued (Table 2) with norfloxacin, ofloxacin and azithromycin (relevant information was not recorded in the studies of ciprofloxacin and cefixime).

Within each event shown in Table 3, the highest event

Table 2 Reasons for discontinuation of medication

Reasons for withdrawal	Number of subjects withdrawn*		
	Norfloxacin	Ofloxacin	Azithromycin
Effective	421	223	29
Not effective	124	90	48
Indication changed	19	15	18
Nausea/vomiting	19	25	12
Rash	8	8	8
Dizziness	7	3	2
Diarrhoea	6	3	5
Abdominal pain	5	0	3
Malaise/lassitude	4	8	1
Headache/migraine	4	4	1
Hospital admission	3	11	7
Allergic reactions	3	2	2
Dyspepsia	2	9	2
Dysuria	2	0	0
Urticaria	2	1	0
Tremor	1	2	0
Glandular fever	0	0	3
Hallucinations	0	2	0
Infection viral	0	0	3
Gout	0	0	2
Others (1 each)	15	23	23
Total	**645**	**429**	**169**

*This information was not recorded for ciprofloxacin and cefixime.

Table 3 Numbers of reports and event rates in the week of administration (W_1) and subsequent 5 weeks (W_2)

Event	Drug	N_1	W^*_1	N_2	W^*_2	W_1-W_2	99%CI
Skin							
Rash							
	Ciprofloxacin	14	1.2	26	0.5	0.8	−0.1–1.6
	Norfloxacin	10	0.9	11	0.2	0.7	0.0–1.5
	Ofloxacin	16	1.5	15	0.3	**1.2**	**0.2–2.1**
	Azithromycin	27	2.4	15	0.3	**2.1**	**0.9–3.3**
	Cefixime	23	2.0	15	0.3	**1.8**	**0.7–2.9**
Psychiatric							
Malaise, lassitude							
	Ciprofloxacin	15	1.3	18	0.3	**1.0**	**0.1–1.9**
	Norfloxacin	9	0.8	8	0.1	0.7	0.0–1.4
	Ofloxacin	15	1.4	14	0.3	**1.1**	**0.2–2.0**
	Azithromycin	5	0.4	12	0.2	0.2	−0.3–0.8
	Cefixime	11	1.0	13	0.2	0.7	0.0–1.5
Central and peripheral nervous system							
Dizziness							
	Ciprofloxacin	11	1.0	13	0.2	0.7	0.0–1.5
	Norfloxacin	13	1.2	11	0.2	**1.0**	**0.1–1.8**
	Ofloxacin	12	1.1	6	0.1	**1.0**	**0.2–1.8**
	Azithromycin	5	0.4	3	0.1	0.4	−0.1–0.9
	Cefixime	7	0.6	14	0.2	0.4	−0.3–1.0
Headache/migraine							
	Ciprofloxacin	8	0.7	25	0.4	0.3	−0.4–0.9
	Norfloxacin	12	1.1	18	0.3	0.8	−0.1–1.6
	Ofloxacin	17	1.5	19	0.3	**1.2**	**0.2–2.2**
	Azithromycin	4	0.4	15	0.3	0.1	−0.4–0.6
	Cefixime	7	0.6	15	0.3	0.4	−0.3–1.0
Alimentary							
Diarrhoea							
	Ciprofloxacin	21	1.8	44	0.8	1.1	0.0–2.1
	Norfloxacin	18	1.6	21	0.4	**1.2**	**0.2–2.3**
	Ofloxacin	10	0.9	24	0.4	0.5	−0.3–1.2
	Azithromycin	18	1.6	20	0.4	**1.2**	**0.2–2.2**
	Cefixime	103	9.2	60	1.1	**8.1**	**5.7–10.4**
Nausea/vomiting							
	Ciprofloxacin	54	4.7	51	0.9	**3.8**	**2.1–5.5**
	Norfloxacin	42	3.8	20	0.4	**3.4**	**1.9–4.9**
	Ofloxacin	54	4.9	25	0.5	**4.4**	**2.7–6.2**
	Azithromycin	31	2.8	17	0.3	**2.4**	**1.2–3.7**
	Cefixime	39	3.5	17	0.3	**3.2**	**1.7–4.6**
Pain abdomen							
	Ciprofloxacin	22	1.9	51	0.9	1.0	−0.1–2.1
	Norfloxacin	24	2.2	34	0.6	**1.5**	**0.4–2.7**
	Ofloxacin	7	0.6	42	0.8	−0.1	−0.8–0.6
	Azithromycin	12	1.1	28	0.5	0.6	−0.3–1.4
	Cefixime	11	1.0	27	0.5	0.5	−0.3–1.3

N_1=the number of events reported in the first week after the start of therapy. W_1=the number of events per 1,000 patients for the first week. N_2=the number of events recorded in the second to sixth weeks after the start of therapy. W_2=the mean number of events per 1,000 patients for the second to sixth weeks

99%CI=99% confidence interval

* For each antibiotic, the denominator used to calculate the rate W_1 is shown in Table 1; the denominator used to calculate the rate W_2 is five times larger as the time period is five times greater.

Highlighted values show events for which the 99% confidence interval for W_1-W_2 is positive and does not include zero.

rates in the first week of therapy were:

9.2	for diarrhoea	with cefixime,
4.9	for nausea/vomiting	with ofloxacin,
2.4	for rash	with azithromycin,
2.2	for abdominal pain	with norfloxacin,
1.5	for headache/migraine	with ofloxacin,
1.4	for malaise/lassitude	with ofloxacin,
1.2	for dizziness	with norfloxacin.

Event rates equal to or greater than 2 per 1000 patients in week 1 were:

ciprofloxacin:	nausea/vomiting	(4.7)
norfloxacin:	nausea/vomiting	(3.8)
	abdominal/pain	(2.2)
ofloxacin:	nausea/vomiting	(4.9)
azithromycin:	nausea/vomiting	(2.8)
	rash	(2.4)
cefixime:	diarrhoea	(9.2)
	nausea/vomiting	(3.5)
	rash	(2.0)

It will be noted that of the relatively more common events recorded in Table 3, the single most frequently reported event was diarrhoea with cefixime (9.2 per thousand patients in the first week of therapy, about 1 in 100 patients).

Vaginitis/vulvitis in weeks 1–6, was reported in 73 females given ciprofloxacin, 64 given norfloxacin, 45 given ofloxacin, 27 who received azithromycin and 30 given cefixime. Thus vaginitis/vulvitis was reported in 1 in 123 women, given one or other of the three 4-quinolones and 1 in 225 women given either azithromycin or cefixime. The greater frequency of vaginitis/vulvitis in women given one or other of the three 4-quinolones reaches significant proportions (χ^2 16.43, $P = <0.001$). Vaginal candidiasis formed the highest proportion of the events making up this term.

The number of reports of uncommon events in the first month after the onset of therapy and considered to be probably or possibly attributable to the drug were:

ciprofloxacin:
anorexia (severe)	1	
convulsions	2	
photosensitivity	1	(2nd case on re-exposure)

norfloxacin:
allergic reaction	4	
angioneurotic oedema	1	
urticaria	1	(2nd case on re-exposure)

ofloxacin:
allergic reaction	3	
angioneurotic oedema	2	
drug interaction (warfarin)	1	

azithromycin:
allergic reaction	2	
erythema multi forme-type blister	1	
poor balance	1	

cefixime:
colitis	2	
colitis pseudo membranous	6	(4 confirmed, 2 unconfirmed including one fatal)
diarrhoea (sanguineous)	1	
exfoliative dermatitis	1	
unsteady on feet	1	

In the studies of the five antibiotics there were no reports of tendonitis, tenosynovitis or tendon rupture in children. As shown in Table 4, tendon disorders were reported in the 2 months following the start of treatment in 20 adults.

In scrutinizing individual reports of possibly iatrogenic illnesses, 17 cases of jaundice or hepatitis occurring after the use of the 4-quinolones were reviewed. Nine of these followed the use of ciprofloxacin, three followed the use of norfloxacin and five followed the use of ofloxacin. All 17 cases either had pre-existing disease (e.g. cirrhosis) or occurred more than 3 months after drug exposure; none was considered attributable to the drug. In the three studies of the 4-quinolones there was only one report of hypoglycaemia during therapy; this patient was an insulin dependent diabetic. There were no reports of haemolytic anaemia or the kind of sensitivity reactions which have been associated with the withdrawn drug, temafloxacin[11].

Pregnancies

As shown in Table 5, a total of 307 pregnancies were reported. Thirty-eight of the 55 women who received these drugs during the first trimester of pregnancy gave birth to healthy babies. No congenital abnormalities were reported.

Deaths

There were 536 deaths in the ciprofloxacin cohort, 445 in the norfloxacin patients, 793 in the ofloxacin cohort, 251 in the patients prescribed azithromycin and 444 in those given cefixime. Thus, 2469 (4.4%) of the total of 56 145 patients included in these five studies died. The major causes of death were cardiovascular and respiratory diseases and cancer. There was one fatal case of unconfirmed pseudomembranous colitis in a patient given cefixime. None of the other 2468 deaths was reported as being due to the antibiotics used in these five studies.

Discussion

Prescription-Event Monitoring provides a numerator (the number of reports of an event) and a denominator (the number of patients prescribed the drug). It collects data during the initial period following the launch of the drug into general practice and does this on a national scale. It allows, therefore, extensive monitoring of the early post-marketing experience of new drugs.

Table 4 Tendon disorders in adults

	Number of reports within 2 months of onset of therapy			
Drug	*Tendinitis*	*Tenosynovitis*	*Tendon rupture*	*Total*
Ciprofloxacin	1	0	0	1
Norfloxacin	2	0	1	3
Ofloxacin	5	3	3	11
Azithromycin	1	1	0	2
Cefixime	2	1	0	3
Total	**11**	**5**	**4**	**20**

Table 5 Pregnancies and their outcome

		Outcome of pregnancies for patients prescribed an antibiotic during the first trimester of pregnancy						
	Overall number of pregnancies reported	*Total pregnancies*	*Normal births*	*Ectopic pregnancy*	*Spontaneous abortions*	*Termination of pregnancy*	*Still births*	*Not known*
Ciprofloxacin	40	9	5	1	1	2	0	0
Norfloxacin	115	13	8	0	2	2	0	1
Ofloxacin	85	10	8	0	1	1	0	0
Azithromycin	29	12	10	1	0	1	0	0
Cefixime	38	11	7	0	2	1	0	1
Total	**307**	**55**	**38**	**2**	**6**	**7**	**0**	**2**

The principal strengths of the technique are that it is a truly observational method in which there is no interference with the decision of the practitioner regarding which drug to prescribe for the individual patient. Doctors are not paid to complete the green forms so there is no resultant incentive to prescribe the drug being monitored. Thus, the selection biases associated with interventional study techniques are minimised. PEM collects all prescriptions issued nationally for the collection period which follows the launch of the drug. It therefore builds up the putative cohort more rapidly than any other method available. It regularly provides information on over 10 000 patients unless the drug being monitored receives only very limited usage in general practice. The method of study provides 'real-world' experience of the use of the drug in everyday practice in which patients are often elderly, with more than one illness and receiving more than one form of medical intervention. PEM provides event data [12] and does not require the practitioner to assess causality or decide whether the event is, in fact, an adverse drug reaction. Finally, the method allows follow-up by access to the life-time medical record of the individual patients.

The limitations of PEM are that the statistical methods relevant to studies involving randomized allocation to treatment are inappropriate and comparisons between drugs have, therefore, to be made with care. The response rate (the percentage of green forms returned) is lower than is desirable and there is no way of showing that the patients whose doctors do return the green forms are not different from those whose doctors do not respond. However, serious bias is unlikely as doctors seem more likely to report, than not report, clinically meaningful adverse experience and, in any case, there is no reason to expect a differential effect when comparing drugs of the same therapeutic class. Furthermore, the response rate is very substantial compared with the proportion of suspected adverse drug reactions notified in spontaneous ADR reporting schemes. PEM is, at present, restricted to experience in general practice and of limited current value in respect of drugs first prescribed in hospital. Finally, the method provides no information on compliance in taking the prescribed medication, although it is known that it was dispensed and available to the named patient.

PEM does not aim to provide a formal assessment of efficacy; however, these studies do show that the outcome of the use of these antibiotics was satisfactory in clinical practice.

Each of these five studies has provided information on over 11 000 patients, thereby substantially appreciating the safety data available on these drugs: the median number of patients represented in the safety data base of Marketing Authorisation (Product Licence) Applications is only 1171 (range 43–15 962 subjects) [13] and few of these patients will be typical of those included in PEM. In these studies PEM has increased the safety database by approximately an order of magnitude.

The results of these studies show extensive use of

azithromycin and cefixime in children (in whom the use of 4-quinolones is considered inappropriate). Use in women exceeds that in men with each of these agents and this is most marked, as is to be expected, with the urinary tract antiseptic, norfloxacin. The event data showed that in the first week following the start of therapy, the adverse effect common to all five of these antibiotics was nausea/vomiting (3 to 5 reports per 1000 patients). Nausea/vomiting may in this study be confounded by indication. Other effects reported in the first week with one or more of these agents included diarrhoea, rash, abdominal pain, headache/migraine, malaise/lassitude and dizziness. Vaginitis/vulvitis (almost always candidial, often delayed until the second or third week), was significantly, more frequently associated with the use of the 4-quinolones than with azithromycin and cefixime.

Uncommon events included rare cases of allergic phenomena, convulsions and pseudomembranous colitis. In these studies tendon disorders were reported in 20 adults within two months following the start of treatment. No cases were observed of the kind of clinical picture (hypoglycaemia, haemolytic anaemia and sensitivity reactions) which has been associated with the withdrawn drug temafloxacin. These antibiotics were given to a total of 55 women in the first trimester of pregnancy; 38 of these pregnancies proceeded to normal births and all of the babies were healthy. There was one fatal case of unconfirmed pseudomembranous colitis in a patient given cefixime. None of the other 2468 deaths was attributed to the antibiotics used in these five studies.

Conclusions

Ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime are acceptably safe antimicrobial agents when used in accordance with their current prescribing information. Nausea and vomiting, other forms of gastro-intestinal intolerance, vaginal candidiasis, and rare cases of allergic reactions, convulsions and pseudo-membranous colitis characterise the adverse reaction profile of these drugs, but all these reactions are relatively uncommon.

No previously undescribed adverse reactions associated with these drugs have been detected in these studies.

Many of the adverse reactions listed in the Data Sheets for these drugs seem to be very uncommon indeed in the everyday clinical use of these agents.

Prescription-Event Monitoring is an effective method of post-marketing surveillance for medicines used in general practice.

References

1 Meyboom RHB, Olsson S, Kuol A, Dekens-Kouter JAM, de Koning GHP. Achilles tendinitis induced by pefloxacin and other fluoroquinolone derivatives. *Pharmaco-epidemiology and Drug Safety*, 1994; **3**: 185–189.

2 British National Formulary, 1995; **30**: 252.

3 Inman WHW. An introduction to Prescription-Event Monitoring. In *Adverse Drug Reactions*. ed Mann RD, Carnforth UK: Parthenon Publishing. 1987: 177–199.

4 Mann RD. Epidemiologic Study Systems: Prescription-Event Monitoring in the UK. *Southampton Med J* 1994; **10**: 12–17.

5 Rawson NSB, Pearce GL, Inman WHW. Prescription-Event Monitoring: Methodology and recent progress. *J Clin Epidemiol* 1990; **43**: 509–22.

6 Johnson NL, Kotz S. Poisson Distribution. In *Discrete Distribution*, Boston: Houghton Mifflin Company, 1969: 87–121.

7 Kubota K, Kubota N, Pearce GL, Prescott P, Mann RD. Signalling drug-induced rash with 36 drugs recently marketed in the United Kingdom and studied by Prescription-Event Monitoring. *Int J Clin Pharmacol Ther* 1995; **33**: 219–225.

8 Andrew JE, Prescott P, Smith TMF, Inman WHW, Kubota K. Testing for Adverse Reactions Using Prescription-Event Monitoring. *Stat Med* 1996; (in press).

9 Council for International Organizations of Medicinal Sciences (CIOMS), World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: 1993.

10 Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In *Textbook of adverse drug reactions*. ed Davis DM, Oxford University Press 1977: 10–31.

11 Anon. Abbott withdraws temafloxacin. *Scrip* 1992; No. 1726: 25.

12 Finney DJ. The design and logic of a monitor of drug use. *J Chron Dis* 1965; **18**: 77.

13 Rawlins MD, Jefferys DB. Study of United Kingdom Product Licence Applications containing new active substances, 1987–9. *Br Med J* 1991; **302**: 223–225.