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Relative Risk of Vaginal Candidiasis After Use of Antibiotics Compared with Antidepressants in Women

Postmarketing Surveillance Data in England

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Abstract

Background: Vaginal candidiasis is a common infection in women. The microflora of the vagina are influenced by a number of factors, including pregnancy, oral contraceptive use, menses and diabetes mellitus. Previous antibiotic use is generally accepted to be a risk factor for vaginal candidiasis but the published evidence to support this is limited.

Aim: To determine the relative risk of vaginal candidiasis following the use of antibiotics compared with antidepressants in prescription-event monitoring (PEM) studies.

Methods: Using data from postmarketing surveillance studies of six antibiotics and six antidepressants, conducted using the observational cohort technique of PEM, the number of reports of vaginal candidiasis was determined in women aged ≥16 years, in each of the first 7 weeks following a prescription for one of these drugs. The relative risks for vaginal candidiasis following the use of these antibiotics and for each of the individual antibiotics compared with antidepressants were calculated for each week and for the overall 7-week period. Women treated with antidepressants were the most suitable comparator group from the PEM database, as they were of a similar age range and the studies were conducted at a similar time period to those of the antibiotics. Also, there was no pharmacological plausibility for vaginal candidiasis being associated with antidepressants.

Results: There were 188 reports of vaginal candidiasis in 31 588 women, aged ≥16 years, treated with antibiotics and 70 in the 45 492 treated with antidepressants. The relative risk for vaginal candidiasis (antibiotic/antidepressants), was highest in the second week, 10.70 (95% CI 4.86–23.55) but was also significantly greater in the first and third weeks after the start of treatment. The risk was also higher in each of the 3 weeks after starting the course for five of the antibiotics,

compared individually to the group treated with antidepressants, the exception being fosfomycin, which had a much smaller cohort.

Conclusion: This study shows a significant increase in the risk of developing vaginal candidiasis following the use of the antibiotics studied (ciprofloxacin, ofloxacin, norfloxacin, cefixime, azithromycin and fosfomycin) compared with that after taking the antidepressants fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine and nefazodine in these PEM studies.

Background

Candidiasis infection is reported to be the second most common cause of vaginitis in women of childbearing age, after anaerobic bacterial vaginosis.[1,2] There is evidence from the US that the incidence of vaginal candidiasis is increasing and although the cause of this remains unclear, numerous factors are known to influence the microflora of the vagina.[1] Common factors that increase the susceptibility to vaginal candidiasis include pregnancy, diabetes mellitus, oral contraceptive use and hormone replacement therapy, which increase the hormonal and glycogen content of the vagina and also its pH.[3] It is also known that vaginal candidiasis increases just prior to menses, which also corresponds with a rise in vaginal pH.[3] Other factors that are reported to increase women's susceptibility to vaginal candidiasis are immune defects, including HIV infection and previous use of certain other medications, for example, immunosuppressive agents and antibiotics.[4-7]

Although there have been reports of vaginal candidiasis in studies of the efficacy and tolerability of antibiotics,[8-11] there are few reports of case-control studies to evaluate the effect of antibiotic use on the prevalence of vaginal candidiasis.[6] There has been one recent study to evaluate the prevalence of antibiotic use in women attending cytology screening clinics.[6] In addition there has been one study to investigate the risk of developing vaginal candidiasis following antibiotic use.[7]

The aim of this study was to investigate whether the risk of vaginal candidiasis was higher in women included in the prescription-event monitoring (PEM) database who had received an antibiotic, compared with those in this database of a similar age who had been treated with another drug.

Methods

The number of reports of vaginal candidiasis were determined in the individual PEM studies of six antibiotics (ciprofloxacin, ofloxacin, norfloxacin, azithromycin, cefixime and fosfomycin) and in the comparator group of six antidepressants (fluvoxamine, fluoxetine, paroxetine, sertraline, venlafaxine and nefazodone). The women who were included in the PEM studies of antidepressant drugs conducted at a similar time period to those of the antibiotics were considered to be the most appropriate comparator group on the PEM database; the age range was similar to those treated with antibiotics and there was no pharmacological plausibility for vaginal candidiasis being associated with antidepressants.

PEM is a non-interventional observational cohort technique used to monitor the safety of newly marketed medicines that have been prescribed by general practitioners (GPs) in England. The patients are identified from dispensed National Health Service prescriptions, details of which are sent to the Drug Safety Research Unit (DSRU) electronically in strict confidence, by the Prescription Pricing Authority for England. Each drug was monitored during its

immediate postmarketing period by sending a questionnaire (called a 'Green Form') to the prescribing GP who was asked to record patients' demographic information and events since starting the drug. Details of this technique have been previously described.[12] The definition of an event is given on the questionnaire and states 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, any alteration of clinical importance in laboratory values or any other complaint that was considered of sufficient importance to enter in the patient's notes".

These studies are records based and conform to the ethical guidelines of the WHO[13] and those of the Royal College of Physicians.[14] The GPs were requested to render the questionnaires anonymous by removing the top portion of the forms before returning them. Event data from these questionnaires were coded using the DSRU dictionary. Doctors' descriptions of events were coded into lower level terms that may be grouped into higher level terms that are arranged in system organ classes. The dictionary is continually updated by the addition of new terms following coding meetings with medically qualified staff.

The age and sex of the patients in the PEM cohorts were recorded, as were the indications for prescribing the drugs. The study cohorts for this analysis consisted of women aged ≥16 years, who had been dispensed the drug of interest and for whom a questionnaire was returned. Women who were reported to be pregnant or to have diabetes at the time of the candidiasis infection were excluded from the analysis, as these were considered to be possible confounding factors.

Analysis

The risk for vaginal candidiasis in the group of women treated with antibiotics was compared with that for women treated with antidepressants during each of the first 7 weeks following the start of treatment and also for the overall period (weeks 1–7). Both the unadjusted relative risk (RR) and that adjusted for age using the Mantel-Haenzel test were calculated for the overall period. For this RR analysis, the cohort was stratified into women aged 16–40 years and those aged >40 years. The RRs of reporting vaginal candidiasis to the GP for women treated with each individual antibiotic compared with the group of women treated with antidepressants were determined. In addition RRs were produced by comparing the risk of vaginal candidiasis in each cohort treated with the individual antibiotics with that in the ciprofloxacin cohort. Statistical significance of the RR were determined using a 2-sided Fisher's exact test. All statistical analyses were performed using STATA® (Release 7.0. Stata Corporation, Texas, 2001).

Results

The 12 individual PEM studies were conducted over a 10-year period, from 1987 to 1997. Each cohort consisted of more than 10 000 patients, with the exception of the fosfomycin cohort, which contained only 3363 patients (table I). The total number of patients treated with an antibiotic (49 478) was less than that prescribed an antidepressant (74 626) [2-sided χ^2 $p < 0.001$]. The antibiotic cohort had a higher number of females aged <16 years of age (6579 compared with 4634 in the antidepressant cohort) and these individuals were excluded from the analysis. Three women treated with antibiotics were also excluded from the subsequent analysis because they developed vaginal candidiasis during their pregnancy. None of the women aged ≥16 years treated with the antidepressants were pregnant at the time of the candidiasis infection. None of the women in the study who developed vaginal candidiasis were known to have diabetes at the time of the infection. After the exclusions, the proportion of

Table I. Study periods, size of cohorts and indication for the 12 prescription-event monitoring (PEM) studies used in this analysis

Drug	PEM study dates prescriptions issued	No. in cohort	No.of females in cohort (%)	No. of females ≥16y (%)[a]
Antibiotics				
Ciprofloxacin	Nov 1988–Jan 1989	11 447	6612 (58)	5750 (50)
Ofloxacin	May 1990–Dec 1991	11 033	6629 (60)	5967 (54)
Norfloxacin	Oct 1990–Oct 1991	11 110	9098 (82)	8312 (75)
Cefixime	Sep 1990–May 1991	11 250	6223 (55)	4320 (38)
Azithromycin	May 1992–Jun 1993	11 275	6575 (58)	4536 (40)
Fosfomycin	Feb 1994–Jun 1996	3363	3033 (90)	2703 (80)
Total		**49 478**	**38 170 (77)**	**31 588 (64)**
Antidepressants				
Fluvoxamine	Feb 1987–Feb 1988	10 983	7694 (70)	6270 (57)
Fluoxetine	Mar 1989–Mar 1990	12 692	8863 (70)	8000 (63)
Sertraline	Jan 1991–Sep 1992	12 734	8729 (69)	8073 (63)
Paroxetine	Mar 1991–Mar 1992	13 741	9279 (68)	8565 (62)
Venlafaxine	May 1995–Jun 1996	12 642	8214 (65)	7444 (59)
Nefazodone	Jan 1996–Feb 1997	11 834	7347 (62)	6690 (57)
Total		**74 626**	**50 126 (67)**	**45 492 (61)**

a Number females aged ≥16 years excluding those who had vaginal candidiasis whilst they were pregnant.

women aged ≥16 years in the two cohorts was similar, 64% (31 588) of those treated with antibiotics and 61% (45 492) of those prescribed antidepressants.

The proportion in each of the two age categories used for the analyses of overall RRs was very similar for both groups of drugs. Of the 31 588 women treated with antibiotics, 11 698 (37%) were aged 16–40 years and 19 890 (63%) were aged >40 years. For those treated with antidepressants, 17 466 (38%) were in the younger age category and 28 026 (62%) in the older age range.

The number of reports of vaginal candidiasis in each of the 12 studies is given in table II. The number of reports was higher in the first 3 weeks following antibiotic use than in the subsequent weeks, and the highest number of reports occurred in the second week after use of these drugs. In contrast, there was no clear pattern to the reports of vaginal candidiasis following the issue of a prescription for an antidepressant. Overall, in the first month following a prescription for an antibiotic, vaginal candidiasis was reported for 139 women (0.44% of cohort of 31 588 women), whereas for those receiving an antidepressant, it was reported for 38 women (0.08% of cohort of 45 492 women).

The risk (number of cases/10 000 patients) of developing vaginal candidiasis for the two drug groups for each of 7 weeks following the start of treatment is given in figure 1.

The risk of developing vaginal candidiasis was higher following antibiotic use than after treatment with antidepressants, in each of the 7 weeks following the start of treatment. The difference between the two groups of drugs, was greatest during the second week.

The RR of developing vaginal candidiasis after antibiotic treatment compared with antidepressant treatment was highest in the second week and this increased risk was statistically significant in weeks 1, 2, 3, 5 and 7 (2-sided Fisher's exact test all p values <0.05) [figure 2].

For both groups of drugs, the risk of developing vaginal candidiasis was statistically higher in the younger women (aged 16–40 years) than in those aged >40 years. The RR for antibiotics was 3.14

(95% CI 2.33–4.24) and for antidepressants it was 3.50 (2.11–5.80).

The overall RR, for antibiotics compared with antidepressants, adjusted for age using the Mantel-Haenzel test, was 3.93 (95% CI 2.98–5.18) very similar to the unadjusted value of 3.87 (2.94–5.09).

The RR with 95% CI, for vaginal candidiasis for each of the antibiotics compared with the group treated with antidepressants is given in table III. A similar pattern emerges to that seen for the combined group of antibiotics. The risk of developing vaginal candidiasis is higher in weeks 1 and 2 for women treated with five of the antibiotics (ciprofloxacin, ofloxacin, norfloxacin, azithromycin and cefixime; 2-sided Fisher's exact test p value <0.05 for all five drugs), than for those treated with antidepressants and also higher in week 3 for three of these drugs (ciprofloxacin, ofloxacin and norfloxacin; 2-sided Fisher's exact test all p-values <0.001). Although the point estimates for fosfomycin in weeks 1 and 2 are higher than that for the antidepressants, these were not significant when tested using a 2-sided Fisher's exact test (p = 0.07 and p = 0.09, respectively), even though the 95% CI suggests statistical significance. This may be due to the cohort for fosfomycin being relatively small and that there were only two reports of vaginal candidiasis in each of these weeks (table II).

The point estimate for the risk (per 10 000 women) for first reports of vaginal candidiasis during the 3 weeks following antibiotic treatment was highest for ciprofloxacin in each week. However, when the RRs for each antibiotic compared with ciprofloxacin were determined, there were no significant differences, with the exception of norfloxacin in week 2, although it should be noted that the 95% CIs around the point estimates are wide. The risk of vaginal candidiasis for norfloxacin was approximately 60% less than that for ciprofloxacin (RR 0.38 95% CI 0.18–0.83; 2-sided Fisher's exact test p = 0.019) [table IV].

Discussion

Although orally administered antibiotics are considered to be one of the common risk factors for vaginal candidiasis, little is known about the fre-

Table II. The number of cases of vaginal candidiasis in each of the 12 prescription-event monitoring studies used in this analysis

Drug	No. females aged ≥16 years[a]	No. first reports of vaginal candidiasis						
		week 1	week 2	week 3	week 4	week 5	week 6	week 7
Antibiotics								
Ciprofloxacin	5750	10	18	11	6	7	4	4
Ofloxacin	5967	4	9	8	3	4	1	5
Norfloxacin	8314	11	10	8	5	5	1	6
Cefixime	4320	5	6	0	3	0	1	0
Azithromycin	4536	3	7	3	2	4	3	2
Fosfomycin	2703	2	2	1	2	2	0	0
Total (%)	**31 588**	**35 (0.11)**	**52 (0.16)**	**31 (0.10)**	**21 (0.07)**	**22 (0.07)**	**10 (0.03)**	**17 (0.05)**
Antidepressants								
Fluvoxamine	6720	1	1	1	2	1	1	2
Fluoxetine	8000	1	0	1	2	3	1	3
Sertraline	8073	0	0	3	2	4	3	3
Paroxetine	8565	3	2	3	3	2	4	1
Venlafaxine	7444	1	1	0	4	0	2	1
Nefazodone	6690	0	3	1	3	0	1	0
Total (%)	**45 492**	**6 (0.01)**	**7 (0.02)**	**9 (0.02)**	**16 (0.04)**	**10 (0.02)**	**12 (0.03)**	**10 (0.02)**

a Number females aged ≥16 years excluding those who had vaginal candidiasis whilst they were pregnant.

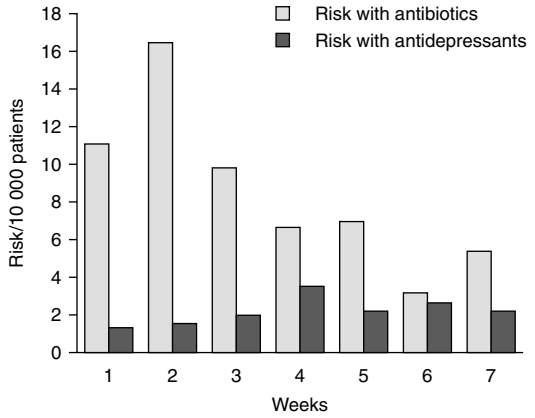

Fig. 1. The risk of developing vaginal candidiasis in women treated with antibiotics or antidepressants.

quency or RR of developing vaginal candidiasis in the general population treated with antibiotics for a range of infections.[7] MacDonald et al. found that there was an excess risk in the first month after antibiotic use compared with the month preceding treatment.[7] In this analysis of historical data from the PEM studies of patients treated with a number of different antibiotics for a range of infections, not only the frequency of developing vaginal candidiasis was determined but also the RR of developing the condition compared with that of women treated with antidepressants. The risk of developing vaginal candidiasis was higher in the first 3 weeks following the start of treatment with antibiotics than in the subsequent 4 weeks. In PEM, no information was obtained on the pre-exposure frequency of the condition, so it was not possible to compare the frequency of this condition in these women prior to the use of the antibiotics. Therefore we selected the most suitable comparator group available from the PEM database, which was women treated with antidepressants as there is no pharmacological plausibility for vaginal candidiasis associated with the use of antidepressants. Also these women had a similar age distribution to that of the cohort of women treated with antibiotics. For the comparator cohort, who had been treated with antidepressants, the proportion of cases reported immediately following the start of treatment (weeks 1–3) was lower than that more than 1 month after the treatment began.

This difference in the pattern of reports of vaginal candidiasis, between the two groups of drugs was shown by calculation of RRs. The overall RR (weeks 1–7) for antibiotic use was nearly four times (RR 3.87; 95% CI 2.94–5.09) that after antidepressant therapy. The increased risk following antibiotic use was significantly greater in each of the first 3 weeks following the start of therapy and was greatest in the second week (RR 10.70; 95% CI 4.86–23.55).

Within each drug group the risk of candida infection was higher for those aged ≤40 years compared with the women aged >40 years. Candidiasis is known to affect women of child-bearing age and rarely occurs before menarche or after menopause.[15,16] A number of factors are known to influence the development of this infection, including sexual activity,[17] use of oral contraceptives,[18] which are more widely used in the younger women than those aged >40 years. Data on the use of oral contraceptives were not collected during PEM studies so it was not possible to adjust for this potential confounder but we have no reason to believe that there would be any difference in the use of oral contraceptives between women given antibiotics and those treated with antidepressants. The role of oral contraceptives in the development of candidia-

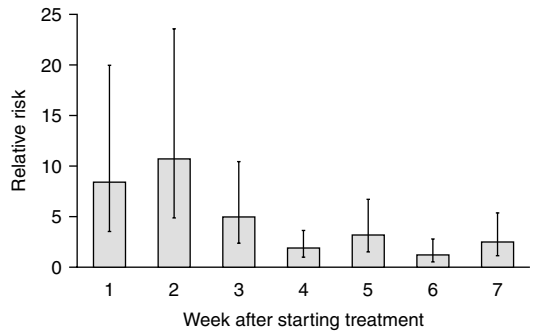

Fig. 2. The relative risk (95% CI) of developing vaginal candidiasis following treatment with antibiotics compared with antidepressants.

Table III. Relative risk (95% CI) for vaginal candidiasis for women treated with individual antibiotics compared with the group treated with antidepressants

Drug	No. of females ≥16 years	Relative risk (95% CI)						
		week 1	week 2	week 3	week 4	week 5	week 6	week 7
Antidepressants	45 492	1	1	1	1	1	1	1
Ciprofloxacin	5750	13.19 (4.79–36.27)	20.34 (8.50–48.69)	9.67 (4.01–23.32)	2.97 (1.16–0.58)	5.54 (2.11–4.54)	2.64 (0.85–8.17)	3.16 (0.99–10.09)
Ofloxacin	5967	5.08 (1.43–18.01)	9.80 (3.65–26.31)	6.78 (2.62–17.56)	1.43 (0.42–4.90)	3.05 (0.96–9.72)	0.64 (0.08–4.89)	3.81 (1.30–11.15)
Norfloxacin	8312	10.03 (3.71–27.12)	7.82 (2.98–20.53)	4.86 (1.88–12.61)	1.71 (0.63–4.67)	2.74 (0.94–8.00)	0.46 (0.06–3.51)	3.28 (1.19–9.03)
Cefixime	4320	8.78 (2.68–28.74)	9.03 (3.03–26.85)		1.97 (0.58–6.77)		0.88 (0.11–6.75)	
Azithromycin	4536	5.01 (1.25–20.04)	10.03 (3.52–28.58)	3.34 (0.91–12.34)	1.25 (0.29–5.45)	4.01 (1.26–12.79)	2.51 (0.71–8.88)	2.01 (0.44–9.15)
Fosfomycin	2703	5.61 (1.13–27.78)	4.81 (1.00–23.14)	1.87 (0.24–14.75)	2.10 (0.48–9.14)	3.37 (0.74–15.35)		

sis is controversial, as others have not found a strong role for oral contraceptives as a confounder and concluded that the risk, if it exists was small.[7,19]

The increased risk for vaginal candidiasis was also found when the individual antibiotics were compared with the group of women receiving antidepressants. Although the point estimates for the risk of developing vaginal candidiasis were higher for ciprofloxacin than for the other antibiotics, no significant difference in the risk for ciprofloxacin compared with the other antibiotics was found, with the exception of the second week following use of norfloxacin. This may be a reflection of the variation in the lengths of courses for these drugs or to differences in the indications, ciprofloxacin is used to treat a range of infections whilst norfloxacin is used for urinary tract infections.[20] Also, the number of reports for certain individual antibiotics was small and hence the 95% CIs around the point estimates are wide.

This was a retrospective analysis of historical cohort data, originally collected to monitor the safety of newly marketed drugs during their early postmarketing period, using the technique of PEM; a large-scale systematic method of postmarketing surveillance covering the whole of England. One of its major strengths is that there are no exclusion criteria for admitting patients to the studies, the only inclusion criteria being that a prescription for the drug was dispensed and the GP returned the questionnaire. Hence selection biases are minimised as there is no interference with the decision of the GPs regarding which drug to prescribe for their individual patients because the patients are identified from dispensed prescriptions. The data were collected from the 'real world' of general medical practice in England. GPs were asked to report events irrespective of whether they considered them to be causally related to the drug being monitored and so the frequency of candida infection found in these studies is likely to reflect that identified in the general

Table IV. Relative risk (95% CI) for vaginal candidiasis for women treated with ciprofloxacin compared with those treated with each of the five other antibiotics

Antibiotic	No. of females	Relative risk (95% CI)		
	≥16 years	week 1	week 2	week 3
Ciprofloxacin	5750	1	1	1
Ofloxacin	5967	0.39 (0.12–1.23)	0.48 (0.22–1.07)	0.70 (0.28–1.74)
Norfloxacin	8312	0.76 (0.32–1.79)	0.38 (0.18–0.83)	0.50 (0.20–1.25)
Cefixime	4320	0.67 (0.23–1.95)	0.44 (0.18–1.12)	
Azithromycin	4536	0.38 (0.10–1.39)	0.49 (0.21–1.18)	0.34 (0.10–1.24)
Fosfomycin	2703	0.43 (0.09–1.94)	0.24 (0.05–1.02)	0.19 (0.02–1.49)

population prescribed these drugs by GPs. Also, it is recognised that women may self treat this infection and such cases are unlikely to be reported to GPs. However, in this study as the women had recently visited their GP they may have had a return appointment, therefore it could be hypothesised that these women would report the vaginal candidiasis to their GP. Under-reporting could have resulted from under-diagnosis by GPs. Moreover, the quality of data reported in PEM is dependent on the GP's skill at filling in the forms. Failure to do this precisely and completely could result in under-reporting or misclassification. However, we have no evidence to indicate that there would be a differential bias in the diagnosis or reporting of this condition between the individual PEM studies. With regard to the diagnosis of vaginal candidiasis in the two groups, we have no means of assessing whether those using antibiotics would be more or less likely to report vaginal candidiasis because it is generally recognised as being associated with antibiotics.

The limitations of the observational technique of PEM have been discussed[12] and include a reporting bias, as no information is available to determine whether the responding GPs or their patients differ from the non-responders. This is a voluntary scheme and GPs are not paid for completing the questionnaires. The response rate following a single posting is on average 60%. This is considered substantial compared with postal surveys to GPs.[21]

There have been a number of case-control studies conducted to investigate the risk factors for developing vaginal candida infection, some of which have been in particular groups of women. However, there have been few studies in the general population to investigate the risk following antibiotic therapy.[7] This study investigated the RR of vaginal candidiasis reported in PEM studies of two groups of newly marketed drugs, antibiotics and antidepressants, prescribed under the conditions of general medical practice.

Conclusion

In these observational cohort studies of women treated in general practice with specific antibiotics or antidepressants, the overall risk of developing vaginal candidiasis was statistically greater after antibiotic use than after the start of antidepressant therapy. This increased risk was higher in the first 3 weeks after the start of treatment and also greater in young women for both groups of drugs than in those aged >40 years.

Although the results from this study should not be extrapolated to all antibiotics, they provide evidence from general medical practice to support the hypothesis that previous antibiotic use is a predisposing factor for the occurrence of vaginal candidiasis.

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