Moxifloxacin prophylaxis in neutropenic patients

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Objectives: Recent studies have shown a beneficial impact of fluoroquinolones on infection-related morbidity and mortality for patients with haematological malignancies during neutropenia. Among the fluoroquinolones moxifloxacin currently provides one of the broadest spectra of antibacterial activity and may be suitable for prophylaxis during neutropenia.

Patients and methods: In this controlled before and after observational study, moxifloxacin chemoprophylaxis was used during prolonged neutropenia in haemat-oncological patients (period 2; 282 episodes). Data were compared with two periods with levofloxacin prophylaxis, one preceding period (period 1; 399 episodes) and a post-observational period (period 3; 53 episodes). Endpoints for evaluation were the rates of Gram-negative and Gram-positive bacteraemia and infection-related mortality.

Results: We found similar survival rates as compared with levofloxacin. The rate of Gram-negative bacteraemia was higher during prophylaxis with moxifloxacin (11%) when compared with levofloxacin (6% for period 1 and 6% for period 3). In addition we observed a marked increase in diarrhoea associated with Clostridium difficile toxin A (CDAD) after a formula change from levofloxacin to moxifloxacin (attack rate 6% versus 33%). A decrease was attained after changing back to levofloxacin and reinforcing hygienic measures (13%).

Conclusions: During moxifloxacin prophylaxis, we observed a significantly increased incidence of Gram-negative bacteraemia and CDAD. Careful attention must be paid not to trade the particularly beneficial effects of fluoroquinolones in the neutropenic setting for such disadvantageous effects. Until further data are obtained, caution is warranted when applying fluoroquinolones with high anaerobic activity in the neutropenic setting.

Keywords: fluoroquinolones, levofloxacin, neutropenia, anaerobes, Clostridium difficile

Introduction

Despite increasing rates of resistance, recent studies have shown a beneficial impact of fluoroquinolones with regard to both infection-related morbidity and mortality for patients with haematological malignancies during neutropenia.1–3 Since 1988, patients with haematological malignancies at our institution have routinely received fluoroquinolones during neutropenia. In a prospective study we recently assessed the impact of discontinuing levofloxacin prophylaxis in an era of increasing fluoroquinolone resistance. Consistent with recent studies, levofloxacin prophylaxis was highly effective for the prevention of Gram-negative bacterial infection during neutropenia1,4 and was associated with decreased mortality.2

Moxifloxacin is another new fluoroquinolone with excellent coverage of Enterobacteriaceae and an extended spectrum of activity against Gram-positive bacteria and anaerobes. It might therefore have an improved efficacy when given as a prophylactic regimen in patients with neutropenia. In the present observational study, we assessed its efficacy by comparing the incidence of
bacteraemia, other infections and mortality in cohorts of patients given moxifloxacin versus levofloxacin.

Patients and methods

In this prospective observational single-centre study levofloxacin prophylaxis (500 mg/day) was employed for 67 weeks (from 1 October 2002 until 28 February 2004, excluding 3 weeks as described previously\(^2\)). This was followed by a period of 50 weeks (from 1 March 2004 until 15 February 2005) during which time moxifloxacin (400 mg/day) was used. Due to concerns of an increasing rate of Gram-negative bacteraemia and CDAD the decision was made to revert back to levofloxacin. This post-observational study period with levofloxacin comprised 19 weeks (from 16 February 2005 until 30 June 2005).

We included all inpatients with leukaemia, lymphoma, multiple myeloma, aplastic anaemia, solid tumours and amyloidosis admitted to our Department of Haematology, Oncology, Rheumatology and Infectious Diseases who had an expected duration of neutropenia of ≥5 days. Patients undergoing allogeneic stem cell transplantation were excluded. Patients were observed from the first day of neutropenia until 2 days after the end of neutropenia. In case of discharge during neutropenia they were followed until discharge and all readmissions were checked. Blood cultures were drawn from all peripheral and central venous lines in the case of fever or clinical symptoms suggestive of an infection. Gram-positive skin-colonizing organisms (i.e. coagulase-negative staphylococci, micrococci or corynebacteria) isolated from blood cultures were considered to be the relevant cause of bloodstream infection only if they were isolated from >1 pair of blood cultures and had identical resistance patterns. MICs for all relevant pathogens were determined by microbroth dilution assays. Breakpoints were interpreted according to NCCLS criteria. All available *Escherichia coli* isolates were typed using PFGE after digestion with *XbaI*.

Stool cultures and analysis of *Clostridium difficile* toxin A was performed in every patient with diarrhoea (EIA Oxoid\(^6\), Wesel, Germany, until 25 August 2004, then VIDAS\(^7\) *C. difficile* Toxin A II, BioMérieux, Nürtlingen, Germany). *C. difficile*-associated diarrhoea (CDAD) was defined as loose bowel movements for ≥2 days in conjunction with a positive *C. difficile* toxin A assay.

At the onset of fever, piperacillin+sulbactam (4 g + 1 g) was initiated as empirical antibiotic treatment immediately after sampling. Antimicrobial treatment was continued until 7 afebrile days during neutropenia or 3 afebrile days after regeneration from neutropenia.

The study protocol complied with ethical principles as specified in the Declaration of Helsinki. Since fluoroquinolone prophylaxis during prolonged neutropenia is the standard of care at our institution, written consent for switching among fluoroquinolones was not considered necessary by the local Ethics Committee.

Results

The cohort of patients given moxifloxacin included 282 neutropenic episodes (Table 1). These were compared with 399 episodes with levofloxacin prophylaxis in period 1 and 53 episodes with levofloxacin prophylaxis in period 3. No differences between the three periods were observed for the median duration of neutropenia, the median patient age or underlying malignancy.

As shown in Table 1, the incidence of Gram-negative bacteraemia per neutropenic episode was higher during prophylaxis with moxifloxacin (11%) than during prophylaxis with levofloxacin (6%).

Table 1. Baseline characteristics and selected outcomes in periods with different prophylactic regimens during neutropenia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study period (prophylaxis with)</th>
<th>1 (levofloxacin)</th>
<th>2 (moxifloxacin)</th>
<th>3 (levofloxacin)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of study period, weeks</td>
<td>67</td>
<td>50</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, no.</td>
<td>241</td>
<td>180</td>
<td>48</td>
<td></td>
<td></td>
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<tr>
<td>Neutropenic episodes, no.</td>
<td>399</td>
<td>282</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of neutropenia per episode, days</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteraemia</td>
<td>22 (6%)</td>
<td>30 (11%)</td>
<td>3 (6%)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>14</td>
<td>26</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other Enterobacteriaceae</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>4</td>
<td>1</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other non-fermentative bacilli</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolone resistance among Gram-negative isolates</td>
<td>15 (68%)</td>
<td>28 (93%)</td>
<td>3 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteraemia</td>
<td>52 (13%)</td>
<td>50 (18%)</td>
<td>7 (13%)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>staphylococci</td>
<td>41</td>
<td>34</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enterococci</td>
<td>8</td>
<td>14</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin/moxifloxacin resistance among Gram-positive isolates</td>
<td>90%/67%</td>
<td>94%/86%</td>
<td>71%/57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea incidence per episode, no. (%)</td>
<td>159 (40%)</td>
<td>132 (47%)</td>
<td>24 (45%)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>CDAD episodes, no. (%)</td>
<td>10 (6%)</td>
<td>43 (33%)</td>
<td>3 (13%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patients with at least one episode of CDAD, no. (%)</td>
<td>10 (4%)</td>
<td>37 (21%)</td>
<td>2 (4%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Overall mortality, no. of patients (%)</td>
<td>18 (8%)</td>
<td>12 (7%)</td>
<td>5 (10%)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Death from infection, no. of patients (%)</td>
<td>10 (4%)</td>
<td>10 (6%)</td>
<td>3 (6%)</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

CDAD, *Clostridium difficile* toxin A-associated diarrhoea.

Statistical significance was tested by ANOVA or $\chi^2$ analysis.

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with levofloxacin (6% for period 1 and period 3). The rate of Gram-positive bacteraemia as well as infection-related and overall mortality did not statistically differ between periods. However, we noted a higher number of bacteraemias due to enterococci during period 2.

Due to a change in the hospital’s discharge policy with shortening of hospital stays, the number of patients discharged during neutropenia rose from study periods 1 to 3 (15% versus 25.5% versus 40.4%). This obviously had no adverse influence on the number of Gram-negative bacteraemias, overall mortality or death from infection.

During prophylaxis with moxifloxacin 26 out of 30 (87%) Gram-negative bacteraemias were caused by *E. coli* and all were fluoroquinolone resistant. The remaining four Gram-negative episodes were caused by *Klebsiella pneumoniae*, *Enterobacter* spp., *Citrobacter freundii* and *Pseudomonas aeruginosa*. During prophylaxis with levofloxacin 14 out of 22 (64%) Gram-negative bacteraemias in period 1 were caused by *E. coli*, all of these being fluoroquinolone resistant. In period 3, Gram-negative bacteraemia was observed in three cases, again all fluoroquinolone resistant. PFGE analysis of available *E. coli* isolates showed no genetically identical strains.

During moxifloxacin prophylaxis, we observed a total of 43 cases of CDAD corresponding to an incidence of 33% per neutropenic episode, which was significantly higher than during prophylaxis with levofloxacin (6% for period 1, and 13% for period 3). Interestingly, the incidence of diarrhoea (any cause) was only slightly elevated, and the difference between the three cohorts was not statistically significant. The difference in the incidence of CDAD was also remarkable and significant if only first episodes (incidence per patient rather than neutropenic episode) were considered (Table 1). After observing an increased rate of CDAD, infection control measures were reinforced, including cohorting of *C. difficile*-positive patients, intensified hand disinfection, wearing gloves and gowns for patient contact, and thorough disinfection of the patients’ environment.

**Discussion**

Compared with the cohorts of patients receiving levofloxacin we observed a tendency towards more Gram-negative bacteraemias and more CDAD in patients given moxifloxacin for infection prevention during neutropenia. The difference in the occurrence of Gram-negative bacteraemias, mostly caused by *E. coli*, was statistically significant, whereas there was no difference regarding overall mortality or infection-related mortality. PFGE typing of *E. coli* isolates gave no indication that nosocomial transmissions were responsible for an increased number of *E. coli* bacteraemias in the moxifloxacin study period. With regard to Gram-positive bacteraemias, moxifloxacin had a better *in vitro* activity against the Gram-positive isolates of all three study periods. This quality, however, did not cause a decrease in the incidence of Gram-positive bacteraemias during moxifloxacin prophylaxis. Moxifloxacin is furthermore characterized by enhanced anaerobic activity as compared with older fluoroquinolones including levofloxacin and we as well as others speculate that this activity might have favoured superinfection with fluoroquinolone-resistant *E. coli* and clostridia in higher titres.6,7 A plausible mechanism underlying this phenomenon is the interference with intestinal colonization resistance through unselective diminution of the protective autochthonous anaerobic flora.7

A coincidence with CDAD was observed in only 7 out of 30 cases of Gram-negative bacteraemia during the moxifloxacin period. The increased incidence of CDAD did not explain the differences in Gram-negative bacteraemia, since a similar frequency of Gram-negative bacteraemia was observed in *C. difficile* cases versus patients with diarrhoea negative for *C. difficile* and control patients without diarrhoea. Furthermore, the higher rate of discharge from the hospital during neutropenia during periods 2 and 3 did not impede an increasing rate of CDAD during period 2. Thus, moxifloxacin was possibly associated with ‘collateral damage’, a term used for ecological adverse effects, such as the induction of CDAD.8 Similar observations were made by Gaynes et al.9 in long-term care facilities using gatifloxacin. In a multivariate model Loo et al.10 showed that the odds ratio for the risk of CDAD was 0.6 for levofloxacin as compared with an odds ratio of 3.4 for gatifloxacin and moxifloxacin.

The number of CDAD in our department significantly decreased after reinstatement of levofloxacin as the prophylactic regimen but did not reach the level of CDAD attained during the initial period with levofloxacin. Persistence of spores in the hospital environment and persistent colonization in low titres of patients later readmitted may be an explanation.

Control of the increased number of cases with CDAD was most likely achieved by a combination of discontinuing moxifloxacin as the contributing agent and controlling for patient-to-patient transmission by reinforcing hygienic measures.

At the time when an increase in CDAD was observed, only the toxin A assay was routinely available and stool cultures for *C. difficile* had not been routinely implemented. Thus, molecular typing to verify the role of patient-to-patient transmission of strains of *C. difficile* was unfortunately not available. In conjunction with reports from the literature6,8,9 the present results warrant further study in order to conclusively evaluate the association between the use of newer fluoroquinolones with increased anaerobic activity and the selection for *C. difficile*.

This observational study investigating prophylaxis in neutropenic patients has shown a higher rate of Gram-negative bacteraemia in the moxifloxacin period than in the levofloxacin period. The large-scale use of fluoroquinolones in this setting may have propelled the selection for *C. difficile*. Careful attention must be paid not to trade the particularly beneficial effects of fluoroquinolones in the neutropenic setting for such disadvantageous effects. This may be particularly true for new fluoroquinolones with high activity against anaerobes. Different therapeutic settings may require different classes of fluoroquinolones. Our observation adds to the more recent understanding that the different fluoroquinolones may not be equally beneficial in different therapeutic settings. Until further data are obtained, caution is warranted when applying fluoroquinolones with high anaerobic activity in the neutropenic setting.

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Transparency declarations

None to declare.

References


