Author's response to reviews

Title: Fluoroquinolone Resistance During 2000-2005: An Observational Study

Authors:

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Version: 3 Date: 12 January 2008

Reviewer's report:

Title: Unexpected Increase in Fluoroquinolone Resistance after Introduction of Moxifloxacin: An Observational Study
Version: 1 Date: 15 November 2007
Reviewer: Joseph M Blondeau

Reviewer's report:

General
This is a well written, well presented manuscript describing an interesting observation with moxifloxacin use and increasing resistance of gram negative bacilli to fluoroquinolones

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Three items of concern to me that I believe require further discussion are as follows:

1) First, the authors refer to moxifloxacin as a 4th generation fluoroquinolone. While this designation is used in the ophthalmic literature, it is not widely used in the systemic infectious diseases literature.

   Changed reference from 4th generation to respiratory when referencing moxifloxacin.

2) The authors also state that moxifloxacin is not excreted in the urine at therapeutic doses, however, it is my recollection that approximately 33% of the dose is excreted renally - can the authors confirm this or refute and reference. With many coliforms, MIC's are low to moxifloxacin (<0.125ug/ml) and as such,
should a third of the dose be renally excreted, there is likely to be urine drug concentrations in excess of these values. Could the authors be asked to deal with this specific issue as part of their arguments - ideally presenting and referencing specific data i.e. pharmacology data and MIC data in text.

Included references in manuscript discussing renal excretion of moxifloxacin, as well as possible causes of resistance that may lead to in vitro susceptibility but in vivo resistance for fluoroquinolones in urine. Also added lab MIC guidelines for FQ against Gram (-) organisms. There is currently no literature directly addressing the efficacy of moxifloxacin for UTIs, however.

3) The third point deals with the specific limitations identified by the authors. The authors state "a causal link between moxifloxacin usage and increasing fluoroquinolone resistance cannot be established" and this relates to the retrospective nature of the study. This one statement is, in my opinion, contradictory to the title which specifies the "unexpected increase in fluoroquinolone resistance after introduction of moxifloxacin" - this title implies moxifloxacin is responsible for the increased resistance. I think more discussion with this point is warranted.

Agree with reviewer¿s point. Changed title to more accurately reflect study design and lack of causal link between moxifloxacin and increasing Gram negative resistance to FQs.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1) under background, the authors indicate moxifloxacin is indicated for community acquired pneumonia. In fact, it is also indicated for therapy for acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, skin and soft tissue infections and now intrabdominal infections in some countries.

Added information to manuscript.

2) in the sentence "Gatifloxacin ws removed from use..., there is a istake with the sentence structure

Corrected grammar.

3) in the sentence "However, it is also excreted at sub-therapeutic doses in the urinary system" I think here specific data needs to be provided along with coliform MIC data.
Added information to manuscript

4) The authors need to be more speculative as to why this observation is seen with moxifloxacin and not ciprofloxacin - is it simply due to urine drug concentrations and if so, how does this fit with the potential for resistance when quinolones are used to treat infections outside the urinary tract and where achievable and sustainable drug concentrations are lower and variable with the various different quinolones used.

Included information on moxifloxacin's excretion compared to other FQs in urine.

5) table 1 and table 2, the organism names should be italicized

Italicized organism names.

6) in figure 1, the graph appears to show a downward trend in quinolone usage over the study period. Moxifloxacin use also declined from 2003 to 2004 and through 2005. Also, ciprofloxacin use also seems to have declined (with fluctuations) over the study period. How as such observations impacted on the data if at all.

While overall FQ use did decline, the percentage of moxifloxacin use to total FQ use stayed roughly constant over the last years of the study (inserted Figure to that effect in manuscript). However, this decline over time would not have biased our study according to our statistician even if moxifloxacin percentage had changed radically.

Reviewer's report

Title: Unexpected Increase in Fluoroquinolone Resistance after Introduction of Moxifloxacin: An Observational Study

Version: 1 Date: 6 November 2007

Reviewer: Lorenzo Drago

Reviewer's report:

General

The authors consider all Gram-negatives isolated from blood cultures for their evaluation. The starting hypothesis is that moxifloxacin low concentrations, as occurs in urinary tract, might select for fluoroquinolones resistance. It is not clear if the isolates included into the study were from patients with urinary tract infections or, at least with colonization, and if they were nosocomial strains.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Were resistant bacteria isolated mostly from patients previously treated with moxifloxacin?

Our study design did not allow for determination of individual patients’ exposure to fluoroquinolones. That would be an interesting follow-up question, which would require substantial resources to answer.

2. No data are provided on ESBL strains. Could the increment of fluoroquinolone resistance be related to spreading of ESBL? It should be interesting at least for E. coli distinguish ESBL+ from ESBL-.

Our lab did not start reporting data on ESBL strains (w/ the exception of Klebsiella pneumoniae) until 2006. Data on ESBL Klebsiella show resistance remaining stable at ~50% from 2003-2004, then increasing to 81% during 2005.

Reviewer’s report
Title: Unexpected Increase in Fluoroquinolone Resistance after Introduction of Moxifloxacin: An Observational Study
Version: 1 Date: 24 October 2007
Reviewer: Po-Ren Hsueh
Reviewer’s report:
1. Not any possible mechanisms were discussed in this article to explain the findings.

Added information to manuscript regarding possible resistance mechanisms with references.

2. Relevant references regarding these findings were not provided.

Added references regarding above. A literature search showed no references directly addressing use of non-primarily renally excreted FQs and increasing Gram negative resistance.

3. The authors should offer the following information
1. Methods for susceptibility testing for the three hospitals.

Added information to manuscript. Susceptibility testing was obtained using standardized MIC determination with a cut-off of <1microgram/ml.

2. Usage of other important classes of antibiotics might have a great influence on fluoroquinolone resistance

FQ cross-resistance has been shown to be clinically induced in laboratory experiments but is not thought to currently play a significant role in FQ resistance
3. Other associated resistant issues, such as MRSA, MDR P. aeruginosa and MDR A. baumannii

MRSA is exceedingly prevalent in our population (~50-60% of all culturable skin and soft tissue infections). However, these questions are outside the scope of our manuscript.

4. The formulations of fluoroquinolones (IV or oral) for each hospital

All three hospitals shared the same formulary with IV and PO forms available. To account for dosing differences between IV and PO for certain FQs (such as cipro), a defined daily dose was calculated adding all IV and PO doses of the same FQ together.

4. Other drawbacks of this study had been described in the Discussion section

Addressed concerns in above comments.

Sincerely,
Paul Sheehan MD/MPH