Author's response to reviews

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

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Author's response to reviews: see over
Reviewer’s report
Title: Fluoroquinolone Resistance During 2000-2005: An Observational Study
Version: 3 Date: 6 February 2008
Reviewer: Joseph M Blondeau

Reviewer’s report:
I have re-reviewed the manuscript and I acknowledge that the authors have made some modifications based on previous comments from my first review. Having said that, I still have some concerns regarding this manuscript and its message. The following are some of my concerns:

1) The authors do acknowledge that some percentage of moxifloxacin is excreted in urine. What drug level does this give as this may be central to the question they are proposing. With low MIC values for moxifloxacin and E.coli (as an example) is there sufficient drug concentrations in urine to inhibit bacterial growth. Second, at the 2007 meeting of ECCMID, Blondeau et al, reported that the mutant prevention concentration of moxifloxacin against E.coli and Klebsiella spp. was from 0.5-2ug/ml; MPC90 of 1ug/ml. These values are similar to what was previously published for ciprofloxacin and levofloxacin by Hansen and Blondeau, Journal of Chemotherapy, 2006. How does such data impact on the arguments. Clearly, moxifloxacin serum drug concentrations would exceed an MPC of 1 ug/ml for the full 24 hours of the doing interval and that was previously published as well.

Response:
Recent North American data from the TRUST 11 study showed that that MIC90 for moxifloxacin against E. Coli was 32 mcg/ml. The TRUST database has 1724 E. Coli isolates from 45 institutions in the US from 01/01/2007 to 07/26/2007. Per BMC ID rules regarding citations, this is included in the text but not referenced as it is unpublished data at this time. Additionally, there is a demonstrated disconnect between in vivo and in vitro antimicrobial activity and the only available data on moxifloxacin concentration in urine comes from healthy volunteers or from a study on prostatitis by Wagenlehner et al that do not evaluate concentration over time.

2) I still have some concerns regarding the title as written and the limitation expressed by the authors that a causal relationship cannot be established.

The title had been changed reflecting the concerns expressed previously. Unfortunately this change was not reflected in the main manuscript and this error has been corrected.

3) In the discussion, the authors state "However, in vivo urine bactericidal concentrations may be much higher than in vitro due to biofilm and pH effects." As well, "Subtherapeutic exposure may result in selection of fluoroquinolone resistant among Gram negative bacteria dwelling in the urinary tract...." I have no idea what these statements in the arguments are trying to suggest. Where is the
biofilm? All antimicrobials have issues with biofilm! Where are the organisms dwelling in the urinary tract - periurethral - ?- and what evidence suggests moxifloxacin is more likely to select for these resistant strains than other quinolones - especially if they already have pre-existing mutations.

The manuscript now includes a citation of the Rosen et al. study showing a surprisingly high incidence of intracellular bacterial communities as well as filamentous bacteria among healthy women with uncomplicated cystitis. Because fluoroquinolone activity is concentration-dependent and the concentration of active drug that reaches the bladder is substantially lower for moxifloxacin than for levofloxacin (Stein et al) or ciprofloxacin this may contribute to selection of resistant strains especially among intermediate-susceptibility strains.

An alternative explanation for the association involves loss of intestinal colonization resistance and was posited in the von Baum et al. article. This phenomenon has been also described in healthy volunteers by Joris et al. using a regimen with similar anaerobic potency.

4) Finally, I do not accept that the manuscript as presented supports the conclusions as written.

The conclusions were changed to reflect that this relationship between FQ use and increasing Gram negative bacteria was an association, as well as a reiteration of the need for follow-up studies.

Sincerely,
Paul Sheehan