Reviewer's report

Title: Probability of Achieving Requisite Pharmacodynamic Exposure for Commonly Prescribed Oral Antimicrobial Regimens against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catharralis Isolated from Adults

Version: 1 Date: 16 April 2011

Reviewer: Michael B Kays

Reviewer's report:

Major Compulsory Revisions

After reading the paper several times, I think there are several issues that must be addressed and explanations provided before I can recommend acceptance of this paper for publication. First, the paper is only relevant for Sao Paulo and cannot be extrapolated to any other city or country globally. The drugs and dosing regimens selected for study were determined from a survey conducted in Sao Paulo, and the dosing regimens are not necessarily recommended today (e.g., levofloxacin 750 mg not included but 250 mg was?). Second, the microbiologic data utilized in the study are old and do not represent resistance rates in any other geographic location. A good example is azithromycin and S. pneumoniae. We haven’t seen >90% susceptibility with this combination in at least 15 years. In many areas of the world, macrolide resistance in S. pneumoniae is # 25%. Therefore, the data presented are not useful to the masses. There are also questions regarding the pharmacodynamic analyses and exactly how they were done (see below). All in all, I cannot recommend acceptance of the manuscript in its present form.

Specific comments

1. Title, page 1 – The title is too long and should be revised. A suggestion is “Pharmacodynamic evaluation of commonly prescribed oral antibiotics . . . .”.

2. Methods

a. Commonly prescribed antimicrobials – as noted above, the authors primarily evaluated dosing regimens that were frequently prescribed in 2006. Although I think this is acceptable, I would also suggest the authors include additional data to show the clinicians what they should be using as well. Is 750 mg of levofloxacin enough? How does levofloxacin 750 mg compare to moxifloxacin 400 mg? What about levofloxacin 500 mg q12h? Why even study levofloxacin 250 mg? Even though clarithromycin was used infrequently, why not include this drug to see if it could be a “better” choice than azithromycin?

b. Microbiologic data (page 4) – I am confused regarding the microbiologic data utilized in the study. First, the MIC data are very old and do not represent current
resistance rates. Second, the authors state that the data were extrapolated from a regional study in 2003-2004 (page 4). However, on page 6, line 2 under Microbiology, the authors list a reference (#23) for the local surveillance study. The reference was published in 2004 but the title mentions 2001-2002. Were the organisms from 2001-2002 or 2003-2004? Clarification is required. Also, the number of isolates selected from the database should only be listed in the Results section, not the Methods and Results as currently done. Lastly, the authors should supply reference(s) for the CLSI recommendations utilized at the end of page 4.

c. Pharmacokinetics (page 5) – In line 4, the authors list criteria for PK studies to be considered. One criterion is the study had to perform adequate PK analysis as determined by the investigators. What criteria were used to determine if the PK analysis was “adequate”. Also, initials for 3 investigators are listed but only 2 authors are listed on the title page and 2 of the investigators on page 5 aren’t listed as authors. Who were these 3 investigators and why are 2 of them not authors? The authors also state that the studies had to present mean and standard deviation results for the PK parameters. However, if one actually reads the reference for the azithromycin data, the authors did not do this. In reference 16, the mean clearance was 122 L/h but these authors did not report standard deviation; they reported relative standard error. Therefore, the authors of the current paper did not execute the methodology as they described. Why? If one is going to calculate AUC/MIC, why not just use the AUC value reported? Which volume of distribution was utilized: Vss, Vc, or some other volume? What other “pertinent” PK parameters were included?

d. Pharmacodynamic analyses (page 5) – How were the serum concentration-time profiles simulated for the beta-lactams using a 2-compartment model with lad time? The authors only provide the reader with clearance and Vc for these drugs. For a 2-compartment simulation, don’t you need data for the microtransfer constants between the central and peripheral compartments (k12, k21)? What about bioavailability? Absorption rate constant? More information is required regarding these simulations. In lines 4-7, the authors state that PD exposures were simulated for the drugs listed against all pathogens but this is clearly not true for cefaclor since it was only studied for S. pneumoniae. This needs to be corrected. Why was total AUC used for azithromycin? Why list the protein binding for azithromycin in Table 3 if total AUC was used? The footnote for Table 3 gives the impression that protein binding for azithromycin were incorporated into the simulations. What exactly was done? What non-compartmental model was applied to calculate AUC/MIC? Why list values for fT>MIC of 20-100% in this section when only 30% and 50% are mentioned in the Results and Discussion. Only these 2 values need to be included. Provide a reference for using 33.7 for the FQs.

3. Discussion – Most of the Discussion section is simply a restatement of the results. The authors need to provide some actual discussion to this section. On page 8, line 8, the authors reference 2 papers and claim improved bacteriologic outcome with levofloxacin 750 mg compared to 500 mg. Were these in vitro
studies or human studies? As written, the sentence seems to suggest better outcomes in patients; however, no current human data has shown this. Later in the first full paragraph, the authors speculate on the PD of levofloxacin 500 mg if the MIC is 0.75 mcg/ml. How much of a difference in target attainment would be expected with this change? The probability may be better but you should make the same assumption with the other agents too.

4. The authors need a paragraph on the limitations of this study.

5. Conclusion – The statement regarding cefaclor is not a conclusion and should be deleted. How is it “fair to say” cefaclor would be better for H. influenzae or M. catarrhalis? Clearly this is speculation at best without any data, which has no place in this section. Why is cefaclor even included in the analysis when all of the regimens listed in Table 1 are < 1%. Cefaclor adds nothing to the paper and should be deleted.

6. In the tables (2-5), I would suggest to list the drug names by drug class. For example, why list azithromycin in between penicillin and amoxicillin? Tables 4 and 5 would be much easier to read if the regimens for the same drug were listed together. Please revise.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.