Author's response to reviews

Title: Pharmacokinetic-pharmacodynamic profiling of four antimicrobials against Gram-negative bacteria collected from Shenyang, China

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Version: 3 Date: 18 May 2010

Author's response to reviews: see over
Dear Editor,

Thank you for the review of our manuscript, MS: 2122684129313081.

Enclosed is a revised manuscript with new line and page numbers in the text, and with grammar and spelling errors corrected. We also responded point by point to each reviewer’s comments as listed below, together with a clear indication of the location of the revision, or inclusion of the revision.

Response to Reviewer's report (Robert G Masterton):

6. Are limitations of the work clearly stated? Yes, but with some exceptions as described below.

Additional limitations of the study are that it does not look at the new carbapenem, doripenem, and neither does it evaluate prolonged or continuous infusion regimens.

Because the new carbapenem, doripenem is unavailable in our region, it is not included in our study, which also does not evaluate prolonged or continuous infusion regimens. This is indeed a limitation that we have clarified in the discussion in Paragraph 5, as follows:

Additional limitations of the study are that it does not look at the new carbapenem, doripenem, and neither does it evaluate prolonged nor continuous infusion regimens.

9. Is the writing acceptable?

Whereas the writing is acceptable there is a need for some editorial revisions.

These are too numerous to mention in detail.

As the reviewer recommended, grammar and spelling errors have been corrected by an expert editor.

Response to Reviewer's report (David Andes):

2. Are the methods appropriate and well described? Most are reasonable. It would be useful to include additional method and result data for the Monte Carlo simulation. As presented, it is very difficult to discern if the modeling sufficient.

We appreciate the reviewer’s critique of this issue. We have added additional descriptions in Methods: Paragraphs 4, 5, 7.

3. Are the data sound? Main drawback is use of healthy volunteer kinetics. The authors sort of acknowledge this in the discussion but then try to say it ok based on an inaccurate statement in the last paragraph of the discussion. Specifically they state that clearance is
reduced in critically ill. Several publications have shown that clearance is often increased in the ICU.

The authors should use population PK data when it is available (it is for most of these compounds).

This section in the Discussion about “healthy volunteer kinetics has been rewritten in Paragraphs 4 and 5 in the revised manuscript, as follows:

There are a few issues that require discussion. With regards to the pharmacokinetic data, the parameters chosen were selected from healthy adults rather than patients. This is due to the lack of comparable pharmacokinetic trials of all these agents in the same patient population; we utilized healthy volunteer data to make a conservative estimate, similar to other studies [2, 9]. Additionally, some studies showed that the pharmacodynamic target attainment calculated with healthy subject pharmacokinetic data was predictive of patient target attainment for the β-lactams [11].

Additional limitations of the study are that it does not look at the new carbapenem, doripenem, and neither does it evaluate prolonged nor continuous infusion regimens.

The authors should show the MIC data, MIC50, MIC90, range

It would be useful to consider extended infusion for the β-lactams

In fact, we did indeed do MIC data, MIC50, MIC90, range analysis, but these data took up quite a bit of room, thus we did not show it in the original manuscript. It is now added in Table 1 in the Additional files section.

Associate Editor comments:

The authors must pay attention while writing names of bacteria, for example, once write Pseudomonas aeruginosa, subsequently write P. aeruginosa. Genus and species name must be italic, or underlined. Besides, authors must write full word first and then write the abbreviation. It is applicable for MIc and other words. These regulations must be followed throughout the text.

We checked the text carefully throughout the manuscript, and corrected errors of the genus and species names of bacteria, MIc and other words in revised manuscript.

Strong recommendation: The English language of this manuscript must be thoroughly edited by expert editor.

As the reviewer recommended, grammar and spelling errors had been corrected by an expert editor.

Abstract: Typographic mistake in first line must be corrected.
As the reviewer recommended, we have corrected this mistake in the abstract, as shown below:

Background:
To examine common antimicrobial regimens used in eradicating certain nosocomial Gram-negative pathogens and determine which ones are likely to be the most suitable as empirical choices in Shenyang, China.

Methods: First para, second sentence: it should be written as Included bacterial strains were Escherichia coli (n=414), Klebsiella (n=236) etc.

This sentence was revised in the first paragraph, second sentence of Methods, as below:

Included bacterial strains were isolates of non-duplicate E. coli (n=414), K. pneumoniae (n=236), E. cloacae (n=40), P. aeruginosa (n=281) and A. baumannii (n=115).

Second para write full word for MIC.

“MIC” stands for minimum inhibitory concentration, which has been added to Background, paragraph 2.

Page4, para 1,2 & 3: The authors must provide short description with reference, so that the readers can try to reproduce similar experiment reading the manuscript. This is very applicable for the readers of the developing countries, who have no access to enough online journals.

What stands for AUC/MIC and %fT.

We have added descriptions in Methods: Paragraphs 4 and 5, as follows

\[ \% fT > MIC = \text{Ln} \left( \frac{\text{Dose} \cdot f}{V_d \cdot \text{MIC}} \right) \times \frac{V_d}{\text{CL}_T} \times \frac{100}{T} \] where Ln is the natural logarithm, f is the fraction of unbound drug, Vd is the volume of distribution in liters at steady state, \( \text{CL}_T \) is the total body clearance in liters per hour, and DI is the dosing interval for the regimen.

AUC/MIC stands for area under the concentration-time curve (AUC) to MIC ratio.

\[ \text{AUC}_{0-24h} = \text{Dose}/\text{CL}_T, \ AUC/\text{MIC} = \text{Dose}\times\text{MIC}/\text{CL}_T \]

The author must describe what is clearance? how to measure it with adequate references.

We have added descriptions in Methods, paragraph 6

“total body plasma clearance was calculated as \( \text{CL} = \text{dose}/\text{AUC}_{0-\infty} \), AUC was determined by the trapezoidal rule and was extrapolated to infinity[4].”

Page 4, para 4: The author must provide description of 'A 5000-patient Monte Carlo'

We have added descriptions in Methods, paragraph 7

“Five thousand estimates of pharmacodynamic exposure were generated for each antibiotic regimen against each bacterial population using values for CLT, Vd, f, and MIC based on probability distributions, as previously described [2].”

Please confirm that ethical approval was granted for the use of the clinical samples in your study, or that none was needed, and include a statement to this effect in your methods.

None of ethical approval for the use of the clinical samples was needed.

We believe that the editors’ comments and our subsequent revisions have made this a stronger paper.

Your consideration for the possible publication of our research is greatly appreciated.

Sincerely,

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