Author's response to reviews

Title: An open prospective study of amikacin pharmacokinetics in critically ill patients during treatment with continuous venovenous haemodiafiltration.

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Author's response to reviews: see over
BMC Pharmacology and Toxicology Editorial Team,

Dear Editorial team,

I am delighted to submit the revised manuscript for the research article ‘An open prospective study of amikacin pharmacokinetics in critically ill patients during treatment with continuous venovenous haemodiafiltration’ (manuscript number 3510487037307299)

The reviewer comments (reproduced below) were most helpful and were addressed as detailed.

Reviewer 1:
- General comments:
The authors have undertaken an interesting study investigating the PK of amikacin in patients receiving CVVHDF treatment. They have outlined their objectives for the study well. I have questions related to the methods and techniques that have been used. The data overall appears sound, however, I have questions related to the prospective vs. retrospective data source. In general the manuscript adheres to required standards; there are some minor issues that need to be addressed. The discussion is long; it needs to be more focused. The conclusion in the abstract and manuscript should be consistent. There needs to be a statement outlining the limitations of the study. There is no obvious statement related to publish or unpublished work by the authors. The title and abstract are appropriate. The overall readability of the manuscript could be improved by removing repetitive statements and content.

Response: We would like to extend our appreciation to reviewer 1 for her very thorough review of our manuscript, and we believe that we have now a much-improved paper based on the advice and suggestions of both reviewers. The discussion has been reduced in length, the manuscript has been restructured (removing repetitive elements also) and the abstract conclusions are now consistent with the manuscript conclusion.

- Major Compulsory Revisions
1. Materials and methods, pg 8-10, PK analysis, I’m a little confused as to why you would use the equations/methods of Sawchuk and Zaske (1976) to calculate out the half-life, k etc when subsequently you used WinNonlin? Also did you use WinNonlin or Phoenix? Why did you not use a non-compartment analysis (NCA) in WinNonlin to do the calculations for the individual PK parameters, all these parameters can be determined using WinNonlin? Subsequently, you used a 1 comp model in WinNonlin to determine PK parameters from multiple serumconcns, but you state that you calculated Vd from Eq 3, t1/2 from Eq 2.
Again I do not understand why you would use the equations to calculate these PK parameters? I don’t know if you’re providing the equations to just show the equations or if you used these and also WinNonlin, the way it is written is confusing. If you used WinNonlin to determine PK parameters then I think the equations are surplus and not needed. It just makes things hard to follow the process of what you did. The methods do not need to list all equations that are done by the software program.

Response: (Also relevant for point 5 below): In a routine clinical setting, a practitioner would not have either multiple serum concentration data from one dosage interval, nor a PK software package such as WinNonlin to work with. Therefore, the Sawchuk and Zaske method was included in order to be able to compare results from the multiple-sample data (and $k$ fitted using WinNonlin) with the more routinely available peak and trough data, analysed using the Sawchuk and Zaske equations. The “peak and trough values” section has been amended to emphasise this. The references to using equations 2 and 3 (6 and 7 in new manuscript) in this section have been removed in the interest of clarity.

As stated in the method section, WinNonlin version 5.2 was used. For data which fits well to a 1-compartment model, there would be no advantage in using an NCA approach, as $k$ would be calculated in a similar manner.

2. Results, 2nd paragraph, Where did the retrospective data come from? The methods describe a prospective study with 5 patients. But the statement here is about retrospective data, which is not in the methods section. How many samples, how many patients did this data come from, where these the same patients? Was this collected at the same institution as the prospective data? Over what time frame was this data collected, was it collected before the change to extended interval dosing, what was the dosing range? Please provide more detail related to this data and clarify its relation to the prospective data.

Response: The data in figure 1 in the original submission was collected from 1 patient from the same institution to illustrate the phenomena of changing levels depending on CVVHDF use. It was collected prior to the prospective study as an example of the type of data which prompted the prospective study. In the interest of clarity and improving the focus of the paper, this figure has now been removed and all references to retrospective data, have been removed.

3. Results, pg 13 1st paragraph, pg 14 2nd paragraph, to be honest I am not really sure that Figure 2 or 3 really contribute anything to the paper, if the authors think they are needed the figures need to be reformatted so the data points in the shaded areas can be seen, it could also be helpful to include a trendline.

Response: The Figures 2 and 3 have been reformatted to ensure that the data points within the target concentration ranges are clear.

4. Results, prospective study, the results outlines in fairly specific detail the PK for each patient, including a transition in dosing from multiple to extended interval, while I appreciate the difficulty in getting PK data from critically ill patients receiving CVVHDF, however, I find it hard to see the generalizability of this data and results to other patients receiving amikacin and CVVHDF. There is no statistical analysis of the data, or any assessment of variability or potential error associated with the collected data. Essentially as the results are presented, it seems 5 patients had PK samples collected and individual PK parameters were
determined. Given the few patient numbers some attention should be given to the limited sample size and potential bias. I would suggest that there are other potential analysis methods that would be better applied to this limited data such as Bayesian estimation, nonparametric analysis (NPAG) or even a non-linear mixed effects approach (NONMEM).

Response: The discussion section now includes a “limitations of the current study” section, which alludes to the small patient number, precluding in-depth statistical analysis, and the fact that these PK parameters are values that might be expected from 5 critically ill patients.

With respect to other approaches, Bayesian, NONMEM etc., data from 5 patients would also be considered to be very limited for these approaches. It could be considered that the data presented in the current model could be informative for future researchers designing a population PK study or for prior estimates for a future Bayesian model, but such analyses are beyond the scope of the current study. The current study is intended to quantify the effect of CVVHDF on amikacin PK, and to show that standard peak and trough data can, and should, be used to determine PK parameters in individual patients, and hence advise on dosage regimens for individual patients.

5. Results, pg 16 as stated in the point above I cannot understand the reasoning for using the Sawchuk and Zaske (1976) equations and WinNonlin, unless for teaching purposes. This distracts from this paper and the objective to add to the very limited literature about what is known about amikacin PK in CVVHDF patients. Table 5 provides a neat summary using the 1 comp and Sawchuk and Zaske, but there is no statistical analysis undertaken that shows any benefit or difference in using both methods to obtain the PK parameters? The numbers presented in the table and text (which is repetitive) on face value are very similar. I would suggest removing all the PK parameter data calculated using the Sawchuk and Zaske method and presenting what was done in WinNonLin, this would tighten the manuscript up and allow it to be more focused, removing the confusion generated by the use of the two approaches. I do not think the purpose behind this manuscript was to compare methodology so unless there is a significant difference or benefit to be seen in using one method over the other, I do not think it contributes anything.

Response: This section has been shortened to omit data which is already presented in Table 2 and 4. The benefit is that Sawchuk Zaske method can be used in practice with standard TDM data (peaks and troughs). This section outlines the feasibility of using routinely available peak and trough data, as part of standard clinical care – whereas multiple doses within a dosage interval would not be measured for every patient. This section along with Tables 2 and 4 illustrates that peak and trough measurements are adequate, along with the Sawchuk and Zaske method, to calculate PK parameters which are comparable with those calculated using multiple doses over the dosage interval.

6. Conclusion, the first sentence is not really a useful statement to be in the conclusion. The conclusion in the manuscript and the conclusion in the abstract do not match, it is always helpful to have consistency between the main manuscript and the abstract.
Response: The conclusions section is now consistent with the conclusions section in
the abstract.

- Minor Essential Revisions
  1. Abstract, background, please consider changing the wording in the following
     sentence “The study population was five…”
     Response: Wording changed as advised

  2. Abstracts, results “normal subjects” what normal subjects are you referring to?
     Is this based on values seen in the literature or a control group? Be careful of use
     of terminology.
     Response: Wording changed (normal referred to subject without renal impairment,
     literature values).

  3. Abstract, conclusion, consider rephrasing the sentence “This is considered a…”
     Are you referring to the use of standard TDM or are you proposing a new type
     of monitoring strategy?
     Response: we are advocating the use of a standard TDM strategy (i.e. peaks and
     troughs) in this specific patient cohort, where TDM may not currently be routinely
     carried out in practice. This last sentence has been amended to clarify.

  4. Background, pg 5, top page, the formatting of the citation [19] needs to be fixed.
     Response: Amended as advised

  5. Materials and methods, 1st paragraph some of the information contained here is
     more suited to being in the results section or a characteristics/demographics
     table. The current Table 1 should be expanded to include information such as
     mean age etc.
     Response: Table 1 now includes mean values. Demographic data moved to the results
     section as appropriate.

  6. Figure 1, please reformat this figure, so that the points in the “target Cmin”
     can be seen more easily.
     Response: Figure 1 from original manuscript has now been omitted

  7. Materials and methods, administration of amikacin, pg 8, the information in the
     background section bottom pg 3 related to peak and trough concs should be
     included here.
     Response: Information moved to appropriate methods section as suggested.

  8. Materials and methods, analytical procedures, what was the LOQ for the assay
     and the CV%.
     Response: Sample analysis was carried out, as is standard practice, by the hospital
     microbiology laboratory. As the data used in the current study was analysed some
     time ago, this method has now been superseded, therefore the LOQ and CV% data is
     no longer available from the hospital laboratory. However, all procedures and
     practices in the hospital laboratory are followed to Clinical Pathology Laboratory
     Accreditation standards.
9. Materials and methods, PK analysis, under multiple conc section. You don’t need to use both concentration and levels. The correct term is concentration – not levels.
Response: Amended as advised

10. Materials and methods, PK analysis, pg 10, the sentence “It should be noted that the study…” should be under the administration of amikacin section, not an afterthought on this page.
Response: Amended as advised

11. Results, patient demographics, as stated before some of the information in the patient section of the material and methods (eg mean age, mean CrCl) should be listed here
Response: Mean age and mean CrCl are now included in Table 1, and the appropriate information from the methods section has been moved to the results section as suggested.

12. Results, 2nd paragraph, I disagree that the significance of amikacin CL is evident on this graph in the way it is currently formatted and think this graph should be reformatted to include a trend line and also make the trough points easier to see.
Response: It is acknowledged that this graph was unclear, however as the retrospective section is now omitted Figure 1 of the original manuscript is now omitted also.

13. Results, prospective study 1st Can you please include a summary of the PK data collected, eg how many total samples, mean (range) of amikacin concs etc. Where any samples BLQ?
Response: This information has now been included as suggested. No samples were BLQ

14. Results, prospective study, pg 12 – 14, much of the information in the paragraphs in this section is in Table 3 and 4, perhaps more came be removed from the text and referred into the Tables, this will remove the very repetitive reading of streams numbers in the text, given the result section is long. I also do not see the benefit of providing all the PK parameters for each individual patient in Table 3 and 4, the mean, SD and range would be just as useful. If there was no real difference in using a two compartment model, I do not see the purpose in provide the individual PK parameters in Table 4.
Response: Tables 2, 3 and 4 now amended to include additional data previously presented in the text, and streams of numbers now removed. Furthermore discussion of individual cases has been shortened to minimise repetition with data presented in the tables. As the text discussing the data from the 2-compartment model has been considerably reduced (as suggested by later by Reviewer 1 in point 22) it is deemed appropriate to keep the information presented in Table 3. (table 4 original manuscript) The individual data is presented in Table 2 (table 3 original manuscript) in order to facilitate direct comparison between the PK parameters for each individual patient using the 1-compartment multiple-concentration method and the Sawchuk-Zaske method. It is considered that a comparison of overall means could obscure differences in calculated parameters for individual patients, therefore individual data in Table 2
has not been removed to illustrate that for each patient the two methods resulted in similar values being calculated.

15. Results, measuring multiple…last paragraph, the block of numbers would be better just being referred to in the table, all these numbers are in Table 3.
Response: This has now been removed and the data is presented in Table 3.

16. Results, pg 15 much of the information of this very long paragraph can be summarized (using Table and Figure) and presented in a far more concise form, the authors belabour the point that the 1 comp was better for most subjects than the 2 comp.
Response: The paragraph concerning fitting to a 2-compartment model has been significantly reduced. As it must be established that a 1-compartment model is adequate in order to use the Sawchuk-Zaske peak/trough method, it is important that the similarity between the results from the 2-compartment model and the 1-compartment model is clear. The data in table 3 (table 4 original manuscript) was retained, as it is helpful for intra-patient comparison of relevant parameters between table 3 and table 2, (table 3 original manuscript) to illustrate the similarity of relevant calculated parameters using the 1-compartment and 2-compartment model, as alluded to in the text.

17. Discussion, pg 17 - 21, the discussion overall is long and there is a fair bit of repetition from the background section. I would suggest making the discussion more focused and reducing the redundancy.
Response: Both the background section (as suggested by reviewer 2) and the discussion section have been reduced and rewritten where appropriate, thus eliminating redundancy.

18. Discussion, pg 18, 1st paragraph, much of this is outlined in the background section
Response: Discussion and background have been restructured to minimise repetition between both sections

19. Discussion, pg 19 2nd paragraph, I’m not sure I’m convinced that this ‘study has demonstrated the value...’ more justification is needed in this paragraph to make this statement. The discussion related to a 2 comp vs 1 comp model does not demonstrate the value of routinely measures concentrations. Please either remove this paragraph or provide the justification for the first sentence.
Response: This paragraph has been rewritten, to highlight the importance of the peak and trough data and the 2-compartment model comment has been omitted.

20. Discussion, pg 19, 3rd paragraph, while what is outlined in this paragraph is indeed important it does not contribute anything to the discussion, particular as there was no assessment or statistical analysis related to these “issues” undertaken in the study.
Response: We agree, the paragraph has therefore been removed.

21. The discussion section should include a summary of limitations associated with the study.
Response: This has now been included at the end of the discussion section
22. Table 2, 3, 4, 5 and 6 – please include a statement of all acronyms used in the table, eg P1A, Cmax etc.
Response: All abbreviations have been described below each table.

- Discretionary Revisions
  1. Background, 2nd paragraph, consider the inclusion of a citation
Response: The information contained therein is readily available from standard texts e.g. Winters Pharmacokinetics or the Renal Drug Handbook

  2. Last paragraph, the sentence “in the hospital setting of this study…” this sentence seems more suitable to be in the methods section.
Response: Amended as advised

  3. Background, pg 6, 2nd paragraph, the paragraphs “The practice prior…” and “The deficit of data…” seem more suitable to be in the methods section.
Response: This information is part of the background to the study, and not methods employed in the current study.

  4. Background, pg 6, the objectives are somewhat wordy and it would be better to make them more concise and to the point, excluding the surplus comments and explanations.
Response: Objectives have been rewritten

  5. Materials and methods, pg 9 please check the formatting of the equations, on the version reviewed the equations are difficult to read as symbols seem to be overlapping and there are thick dark “brackets” covering symbols.
Response: Formatting checked on resubmission

  6. Results, prospective study, Is “Estimate of PK parameters…” a sentence, heading or statement?
Response: This sentence is now italicised to be consistent with the other subheadings in this section

  7. Results, amikacin CL due CVVHDF, last paragraph, this last paragraph seems to contain the most important and potentially relevant information from the study and I would suggest these results should be emphasised more and perhaps move more to the front of the results.
Response: This is an important point, and the suggestion is well received. However, as the PK parameters i.e. TBC need to be calculated initially in order to calculate the fraction of clearance via CVVHDF, it makes sense to present the PK parameters first. However, further reference to this point has been made at the beginning of the discussion.

  8. Discussion, 2nd paragraph, there is no use of Ideal body weight or weight in the earlier part of the manuscript or the results in relation to the estimation of the PK parameters in this study, perhaps a conversion to L/kg should be outlined in the results.
Response: Weighing of patients was not undertaken during this study. The logistical difficulties of weighing acutely and critically ill patients made it unfeasible.

9. Discussion, overall comment, it would be interesting to undertake a PK analysis to look at the statistical significance of type of therapy, flow rate and types of filters to determine the variability and influence on the PK parameters.

Response: It is agreed that this is certainly an issue of great interest. The following sentence is already in the discussion at the point where CVVHDF conditions are discussed:

“Therefore a more comprehensive study of CVVHDF parameters employed and amikacin levels is warranted to clarify the effect of CVVHDF conditions employed on amikacin clearance”.

Reviewer 2

- General comments.
  Overall, I had difficulty following or working my way through the details as written for the background, methods and results. The discussion has areas that need to be edited such as the first paragraph and others that explain the authors thoughts very well such as the paragraph starting with “once daily” on page 18. The authors seem to over-explain concepts that are well-described in the literature such as drug half-life “on” and “off” dialysis yet do not adequately explain other areas for instance why was there “no discernable distribution phase” as reported on page 15? But then use phrases such as “which is generally slightly higher than” (page 15).
  The authors need to decide the target audience of this paper? Clinicians? Pharmacokinetic Professors?

Response: We would like to extend our appreciation to reviewer 2 for her very thorough review of our manuscript, and we believe that we have now a much-improved paper based on the advice and suggestions of both reviewers. The discussion has been reduced in length, the manuscript has been restructured (removing repetitive elements also) and the abstract conclusions are now consistent with the manuscript conclusion. This paragraph referred to above (pg 15 of original submission) has now been revised and reduced in length. The lack of a discernable distribution phase is simply due to distribution happening very quickly in the sample patient group, and where it was evident the magnitude of the distribution phase was small. This paragraph has been added to in order to explain this observation.

1. Background: Overall goal of the study is stated but the objectives as written are not clear or concise. For example: objective (a) on page 6 as written is not a specific study object but a paragraph describing methods. Objective (b) is several objectives (also serum level concentrations is an incorrect use of the terms). The authors need to concisely define and state the study objectives.

Response: Study objectives have been rewritten as advised.

2. The remaining details should be presented concisely in the methods. The background is very long as though I was reading a review paper but then realized there was a methods section. Much of the background material is not necessary. The reader does not need a full history of amikacin studies in CRRT.
Response: Background and certain sections of the discussion have been revised to make the manuscript more focussed and also to eliminate repetition between background and discussion.

3. Methods - The authors did not describe how the data represented in figure 1 was acquired or how the patients were identified. 
Response: The data in figure 1 in the original submission was collected from 1 patient from the same institution to illustrate the phenomena of changing levels depending on CVVHDF use. It was collected prior to the prospective study as an example of the type of data which prompted the prospective study. In the interest of clarity and improving the focus of the paper, this figure has now been removed and all reference to retrospective data, have been removed.

4. Methods - After the blood samples were attained how were the samples processed and stored? Describe briefly in 1-2 sentences 
Response: Samples were stored at 4 degrees prior to prompt analysis (by the hospital microbiology laboratory). This information has been included in the methods section.

5. Methods - Page 8 under Analytical Procedure paragraph 2 is confusing as written. 
Response: Paragraph 2 has been reworded.

6. Methods - The small number of patients enrolled (n=5). Also, the amikacin dosing strategy changed during the study period for 3 of the participants so the patient sample is n=3 and n=2? 
Response: A limitations section has now included at the end of the discussion section. The difference in dosing strategy does not impact the measurement of pharmacokinetic parameters –it is highlighted merely to explain why the initial dose for those patients might seem different to what would be recommended following a pharmacokinetic consultation.

7. Results: Page 11 paragraph 2. “The effect of CVVHDF therapy…. This data could be stated in 1-2 concise sentences but same basic idea which is well-described in the literature that once CRRT is stopped the drug half-life increases is repeated several times as if it is a new idea. 
Response: Retrospective data is now omitted.

8. Perhaps this should be written as a case series since some of the data appears to be reported as a case series. 
Response: Information on each individual case has been reduced in the text.

9. Results - Page 14 last paragraph estimates of PK parameters should be put in a table. 
Response: This data has now been moved to Table 2.

10. Results - Tables and figure: My opinion is there are too many tables and that data in the tables should not be reported extensively in the results and again in the discussion section. 
Response: Much of the data presented in the text has now been moved to the tables (also on recommendation from reviewer 1). Furthermore, table 5 of the original
manuscript has been removed, as the data in tables 2 and 3 (now 2 and 4) were adequate for the purpose intended from the original table 5.

11. Table 2 - title instead of using TDM perhaps state that is was from multiple doses and samples?
Response: The title of table 2 (now table 4) has been changed.

12. Review the figures. It appears that there is a problem with your data. Hours are listed on the “X” axis which would mean the patients were followed for more than 200 hours or maybe a decimal was left off.
Response: Peak and trough data were recorded for a number of days – there is one dose daily approximately (except patient 4 who had twice daily dosing). The peak and trough data used to calculate the pharmacokinetic parameters presented in the current work was not necessarily the first dose (rather around the time that the patient was recruited to the study for the multiple serum samples to be taken, the patient may not have been on the ICU prior to this time) – but in Figures 2 and 3 in the original manuscript (Figures 1 and 2 in the new manuscript), peak and trough data are presented for a number of days following the first dose – hence the range of approximately 200 h commencement of therapy.

As a research group we are very excited and delighted to be afforded the opportunity to disseminate our findings through your publication.

We look forward to your favourable consideration,
Kind regards,

Dr Maria Donnelly