Reviewer's report

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

Version: 3 Date: 31 July 2012

Reviewer: Catherine MT Sherwin

Reviewer's report:

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

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 There is no obvious statement related to publish or unpublished work by the authors.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.

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 serum concs, 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.

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.

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.

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).

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 equations 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.

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.

Minor Essential Revisions

7) Abstract, background, please consider changing the wording in the following sentence “The study population was five…”

8) 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.

9) 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?

10) Background, pg 5, top page, the formatting of the citation [19] needs to be fixed.

11) 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.

12) Figure 1, please reformat this figure, so that the points in the “target Cmin” can be seen more easily.

13) 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.

14) Materials and methods, analytical procedures, what was the LOQ for the assay and the CV%?

15) 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.

16) 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.

17) 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.

18) 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.

19) 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?

20) 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.

21) 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.

22) 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.

23) 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.

24) Discussion, pg 18, 1st paragraph, much of this is outlined in the background section.

25) 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.

26) 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.

27) The discussion section should include a summary of limitations associated with the study.

28) Table 2, 3, 4, 5 and 6 – please include a statement of all acronyms used in the table, eg P1A, Cmax etc.

Discretionary Revisions

29) Background, 2nd paragraph, consider the inclusion of a citation

30) Last paragraph, the sentence “in the hospital setting of this study...” this sentence seems more suitable to be in the methods section.

31) Background, pg 6, 2nd paragraph, the paragraphs “The practice prior...” and “The deficit of data...” seem more suitable to be in the methods section.

32) 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.

33) 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.

34) Results, prospective study, Is “Estimate of PK parameters...” a sentence, heading or statement?

35) 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 emphasized more and perhaps move more to the front of the results.
36) 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.

37) 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.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.