Author’s response to reviews

Title: Covariates of intravenous paracetamol pharmacokinetics in adults

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Author’s response to reviews: see over
Materials and methods.

1. A table with key descriptive information of the 7 different studies would assist the reader in evaluating the degree of heterogeneity, i.e., age (median, range), weight (median, range), FFM (median, range), sex, duration of sampling, assay method.

2. Page 7 – typo: RUV is defined as both residual unexplained variability and residual unidentified variability.

3. Page 8 – please explain in the text why a 2 compartment model was assumed not evaluated against other models (1 or 3 compartments).

4. Was a step-wise procedure used for the addition of covariates or were they tested in stages (i.e., size descriptors first)?

5. Page 10 – was the bootstrap stratified according to study or any covariate?

Results

6. There is no text regarding model evaluation (see note below regarding table 1).

Discussion

7. All healthy subjects were aged below 37 years old. As age is a significant covariate in the model this potential bias should be discussed.

8. Page 13, paragraph 3 – change in fat per kilogram body weight is used to explain the change in V noted with age. Given the presented model tries to account for such changes with the use of NFM are the authors indicating that this size descriptor is not able to explain the increased fat percentage noted with age, and therefore, is there another size descriptor which would perform better and be able to account for these changes?

9. Page 14, paragraph 1 – the greater increase in CL in pregnancy (1.58 vs 1.23) noted in reference 45 may in part be caused by the fact that a size descriptor was not utilised and the pregnant women were larger. The conclusion of reference 46 states “… the absorption and disposition of acetaminophen, when used in a standard oral dose, are not affected by pregnancy,” and therefore need further explanation in the discussion. It is current location the reference is misrepresented.
of overlap of the shaded areas is not clear
Discretionary Revisions
Materials and methods.
1. Page 9 – please indicate in the text that a linear model is used for the effect of age on CL and V
Results
2. The change in OFV for the different size models is included however it would be useful to present the same information for other significant covariate relationships.
Discussion
3. Page 13, paragraph 1 – were the authors expecting a gender effect on clearance?
4. Page 13, paragraph 2 – the authors could include the estimates from paediatric data to illustrate the similarity with the present pooled analysis
5. Page 15, paragraph – the authors introduce the concept of unexplained vs explained parameter variability here. It may be worthwhile to include these terms in the methods section. It would be informative to know the extent of explained parameter variability, the values of BSV/BOV for CL and V without any covariates could be included for this comparison.
Figures
6. Figure 1: the y axis could be a semi-log plot could be used to better visualise the VPC

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

Reviewer's report
Title: Covariates of intravenous paracetamol pharmacokinetics in adults
Version: 1 Date: 7 July 2014
Reviewer: Douglas Eleveld
Reviewer's report:
This review concerns "Covariates of intravenous paracetamol pharmacokinetics in adults". Overall the manuscript is informative, easy to read and quite well written. I do have some suggestions or perspectives for the authors. I have no comments which I would consider Major Compulsory Revisions.
The primary goal of the model development seems to be able to make out-of-sample predictions. To determine whether this goal has been achieved to a reasonable extent there should be a measure of this somewhere. MdPE and MdAPE as described by Varvel, although certainly not perfect for this purpose, are used widely. Using MdPE and MdAPE would additionally allow the relative prediction accuracy of this model to be roughly compared with that of other drugs. This may contribute some useful perspective regarding the utility of dose adjustment of paracetamol compared to other drugs, a topic which the authors already touch upon in the discussion.
An explicit statement of the parameter equations for the final model would be
very helpful to ease interpretation. It would be just a few lines and really make understanding the final model much easier. In the current state one has to do considerable searching in the text to collect all the relevant terms. Probably for the authors this might seem unnecessary, but I think it would really help readers trying to understand the material for the first time.

Some of the covariate relationships accepted into the final model are only supported by a single study. There is the possibility that differences in how the particular study was performed might be behind the apparent differences for a covariate which uniquely identifies individuals from that single study. For example, perhaps orthopaedic patients are more likely to receive certain medications which could influence their paracetamol PK. Did the authors consider this possibility? How was this addressed?

Model structures are often based on physiological insight. It is not sensible to re-estimate these model structures for every analysis. In this sense, the current investigation handles allometry scaling constants correctly, using the fixed theoretical values and not trying to estimate these from this particular dataset. I think this is the correct approach. However, in NONMEM, ETAs represent variability of unknown origin. If the origin of the variability was known it would be in the structural model. How does it help model derivation to assert that two random variables of unknown origin have an estimated relationship? What does it mean to estimate a relationship between to unknowns? I understand the temptation to include correlations it in the model since AIC is often significantly lower. But AIC alone cannot be used as a good argument here. If AIC was the final arbiter then by the same argumentation it would also make sense to estimate allometric scaling constants. I would like to make it clear that I do not object to the estimation of the correlation coefficients. But I would like to hear and I think readers would like to hear good physiological arguments as to why parameter correlations should be estimated. Can the authors comment on this?

Discussion, second paragraph: Please qualify more clearly what you mean by “the same as those predicted from paediatric data using allometry”. Is this a suggestion that this model extrapolates well to paediatric data and that previous paediatric model extrapolates well to these groups as well? I think this is extremely interesting and deserves more attention here. Can the degree of agreement between these two very different model derivations be more clearly quantified?

I noticed that a number of the authors of the current study are also authors of the mentioned paper (reference 15). If it is possible to estimate a combined model from the datasets considered in both these studies then I suspect such an analysis would be even better for identifying covariate relationships than the “all adults” approach of the current study. The comment in the discussion suggests that the models are for the most part compatible and that a combined model might not be much more technically difficult than the current approach. I would like to encourage the authors to consider this approach.

Minor comments:

I would like to see more information about the spread of demographics. A histogram would be helpful here. A “flat” distribution in age and weight would improve confidence that the covariate relationships found are real physiological phenomena. Otherwise, (comparably) small portions of the age- or weight-range can dominate AIC and influence the covariate relationships selected as statistically significant.
The current manuscript addresses covariate relationships in the PK model, and the PD model is not considered. However, the conclusion regarding model adjustments for covariate relationships should consider or at least mention the possibility of covariate relationships in the PD which could (at least conceivably) make dose individualization more promising than stated. The conclusion that dose individualization is not necessary should address that the PD part is technically missing here.

In the methods, the assay accuracy of these individual studies is mentioned in detail. Was anything done with these values? Was a single residual error estimated for all studies? If there are important differences between the assay accuracy of the studies, shouldn’t residual error be estimated separately for each study? This would be cleared up if the final equations were stated explicitly. Are there any indications that patients and volunteers differ in their PK model? In general, patients receive more co-medications and are likely to have poorer health. Possibly the current dataset is not sufficient to clearly address this.

By a proportional variance model for the structural model parameters, I presume they mean the usual assumption of log normal distribution was made i.e. *EXP(ETA()) as is done for the majority of NONMEM models. Is this correct? An explicit statement of the final model equations would be helpful here.

Did the authors consider compartmental allometry here? (Eleved DJ, Proost JH, Cortínez LI, Absalom AR, Struys MM. A general purpose pharmacokinetic model for propofol. Anesth Analg. 2014 Jun;118(6):1221-37.) In this case, scaling Q2 to the 3/4 power of the estimated V2 divided by the reference V2 value?

Is there any particular reason that linear age model was considered instead of exponential or power models? Linear models can in some cases have poor extrapolation properties and this is often suggestive of over-fitting.

In Table 1, the lower 95% CI bound for FfatCL is zero. Shouldn’t then FfatCL have been removed from the model?

In Figure 2 the 90% CI prediction interval stops after 12 hours while the rest of the lines continue to 36 hours. Why are the lines differentiated in this way? Perhaps it is a PDF issue but only the first 12 hours of the 90% CI is shaded while the rest is not. It is unclear why this is.

**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