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A comparison of different methods for the first-in-pediatric dose selection

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A Comparison of Different Methods for the First-in-Pediatric Dose Selection
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Dear Clinical Pharmacologist Mahmood,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Sep 06, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

EDITOR: As you will see, the reviewers argue that your model is of interest to the scientific community but that your approach suffers from technical deficiencies that are outside of the realm of technical issues of model predictions per se. One main concern is that the model is descriptive rather than predictive (reviewer 2) and that the model lacks prospective validation (reviewers 1 and 2). Furthermore, we would like you to explicitly and clearly elaborate on the discriminating aspects of your model relative to other, more putative models used for PBPK. These requests, which are non-negotiable in terms of the acceptance of your paper, come on top of the other valid points raised by the reviewers and account for the necessity of an extensive revision of your work.

Reviewer #1: The research topic is of high importance and interest for scientific community. However, I have following questions and concerns that should be considered for scientific robustness of the work.

Please differentiate oral and IV doses in the data. Authors failed to discuss role of bioavailability and focused predominantly on clearance.

Authors discussed and suitably estimated/chosen exponents for clearance and BW based methods. This is expected to improve the performance of the data on which the estimate of exponent was chosen for.

I highly encourage the authors to have independent test set.

Authors should at least attempt to understand the clearance mechanisms especially if drugs are predominantly really cleared or metabolized before attempting to compare such wide range of methods. It will help to know how different method worked for renally cleared vs metabolically cleared drugs.

Having simple exponent fitting may appear good statistically especially when applied on the same data where exponent was identified or fitted. Pediatric dose estimation was as easy as changing exponent from 0.75 to 0.9, this complex research topic would have been solved decaded ago. I would appreciate if authors can give due credit to scientific complexity involved in such research area than to simplify the conclusion to simple change in exponent solving the issue.

PBPK models are based on scientific knowledge we have on maturation of human body, enzymes and other physiological processes. Scientifically there are many gaps in our knowledge hence it is conceivable PBPK may not resolve the challenges of pediatric dose finding especially neonatal. However, I have strong reservations on the conclusions authors have drawn about PBPK vs simpler methods based on limited research methodology they have employed. In all simpler approaches, authors fitted or fudged exponent or other

parameters of the model to make the predictions look good on the same data for which it was fitted. On the other hand, PBPK models were gathered from literature and in many cases the purpose of those models was not pediatric dose finding. If authors want to do scientific comparison, they need well-defined modelling data set and their own PBPK model building or choosing suitable cases from literature. With such limited and biased methodology, I would strongly recommend the authors conclude suitably without demeriting any of the approach. Authors need more independent testing of approaches on independent data set to make meaningful conclusion on comparisons.

Some technical comments:

Language is difficult to follow, please have a English language-proofing.

Line 54 - It should be equation 4.

Equation 5 - what is the rationale for applying exponent again when it was already applied to clearance in equation 4. Authors should provde biological or scientific explanantion than to find exponents that may fit the data they are seeing. Otherwise validate the equation on independent data set.

Lines 56-59 - Please cite and read original references than to base your work on indirect references, at least when citing the method by name.

Reviewer #2: Dear Author,

With pleasure I have read your manuscript. I believe it is of high value to compare different approaches to derive dosing regimen to our vulnerable pediatric population.
Allometry or other simple approaches that are using allometry has it's pro's and con's versus mechanistic models such as PBPK models (which btw are not empirical/data driven models which you are stating). However, methodologically it seems that the methods you have applied (such as the usage of a 0.9 exponent) seem more to be data driven rather than having a physiological meaning, using too few drugs to really make a statement. Depending on the included drug with its pk characteristics, the result may be completely different. Additionally, instead of retrospective comparison of actual data, the resulting doses are compared, and mean clearance values.
Also, there are other papers out there clearly showing the opposite statement that allometry does not work. As you have also shown in your manuscript, especially in the newborn, where maturation of active processes, and rapid changes of body composition occurs, simple allometry does not properly predict exposure in children. What I also agree from your introduction, that pathophysiology may also completely differ from that of adults which is another aspect that one would need to consider, that is lacking when applying these simple methods. For this reason, I was not convinced that with the few drugs being selected for testing, simple methods would suffice or be equally well predicting for First in pediatric doses selection.

Reviewer #3: 1. Does adult dose come from FDA labels? The observed dose of pediatrics seems to have multiple sources, so how to determine which source of data to choose for statistical analysis in this study?

2. Although PBPK models were obtained from literature, but what kind of computer software was used for data calculation when using of PBPK models in this study, was it the same with the obtained literature?

3. On page 4, the two formulas in method 2A were not clear.

4. There were other pediatric dosing rules such as Clark's Rule (2-17 years), Clark's Surface Area rule, Young's rule, Webster's rule, Fried's Rule, and Shirkey's BSA Recommendation, although some studies have shown that they might be unreliable, now that they had been published and used, why comparing the rules with the four methods in this article to see if there is a big difference.

5. How many observed dose(s) of pediatrics were from the FDA labels? For labels with both adult dose and pediatric dose, which rule gives a better prediction?

6.What was the source of 113 observations across the age groups? Was there multiple data sources for a same drug? If there were multiple observations for a same drug, and the differences between each observation were small, the reliability of statistical results of this study will be seriously affected. In other words, multiple approximate data for a same drug may affect the percent prediction error result.

7. The author needs to further explain the sources of the data in the paper.

8. Do not see the percent prediction error of the whole body PBPK rule?

Author's response

EDITOR: As you will see, the reviewers argue that your model is of interest to the scientific community but that your approach suffers from technical deficiencies that are outside of the realm of technical issues of model predictions per se. One main concern is that the model is descriptive rather than predictive (reviewer 2) and that the model lacks prospective validation (reviewers 1 and 2). Furthermore, we would like you to explicitly and clearly elaborate on the discriminating aspects of your model relative to other, more putative models used for PBPK. These requests, which are non-negotiable in terms of the acceptance of your paper, come on top of the other valid points raised by the reviewers and account for the necessity of an extensive revision of your work.

Dear Dr. Heger,
Thank you very much for sending me the comments of the reviewers and giving me the opportunity to respond. I will respond to this and to your comments. The two reviewers did not understand the methodology at all despite I gave references for each method or model. I have explained the methodology to the reviewers in my response. I can barely make any change in this manuscript because the methodology was misunderstood and the rest of the comments are trivial and subjective but I have responded to these comments. You will see how little changes I can make in the manuscript based on the reviewers' comments and my

response. In any case, I have made some changes and these are highlighted in red. The changes are in methodology section to emphasize a reader that the models in this study were not developed from the data used in this study and shortened my comments on radiprodil and remdesivir under section 5, 'Comparison between Whole Body PBPK modeling and the proposed methods for the Pediatric Dose Projection' . I have added four more references (91, 101-102, 106).

There is no technical deficiency in this manuscript. In this study, I did not develop any model from the drugs I used for my analysis rather these are published models and references were provided in the manuscript. The reviewers just simply did not bother to look at the references for the models or try to understand the methodology.

Method 1: Several years ago (reference 2 was published in 2014 and has the description of this model), I developed this method as a compromise between exponent 0.75 and 1.0 because these two exponents were not found suitable across all ages (references 2, 8, 9, 83). Exponent 0.75 and 1.0 are well known allometric exponents for the prediction of clearance and dose (reference 2) and are in existence since decades. In fact, exponent 1.0 is used for dose prediction in children directly extrapolated from adult dose (per kg body weight basis) and is very well known. In this study, I used exponent 0.9 for dose prediction based on previous analysis not using the data from this study.

Method 2: Salisbury Rule was developed by Lack and Stuart in 1997 (reference 10). They developed the model based on their data and I simply used their equations 3 and 4 for my analysis (validation of their method on the drugs I used in my analysis). It is clearly written that "This method was proposed by Lack and Stuart-Taylor and is as follows (10)" (equations 3 & 4). Lack and Stuart-Taylor had already validated their method and found the method's predictive power acceptable (10).

Method 3: I developed this model called Age Dependent Exponent (ADE) model several years ago and the model was previously used for the prediction of clearance across the age groups including preterm neonates (references 2, 8, 88-91, 101). This method was also described in reference 2 published in 2014.
Now, you can see that I used previously developed models and used these models for the prediction of clearance or dose in this study. The purpose was to compare the Salisbury Rule with other methods. Salisbury Rule is very simple and I find no reason not to explore it and compare it with other methods including well known PBPK model. All models used in this study are predictive not descriptive because these models were previously developed and were not developed in this study or data from this study.

You wrote that "Furthermore, we would like you to explicitly and clearly elaborate on the discriminating aspects of your model relative to other, more putative models used for PBPK".

I do not know what are 'discriminating aspects'?

If I understand correctly, you are pointing to the comment of Reviewer 1 who writes that "I would strongly recommend the authors conclude suitably without demeriting any of the approach".

I think that my conclusions are correct and suitable based on the data. I did not demerit any model rather I based my conclusions on my analysis which I believe is correct analysis as I mentioned above. I have requested Reviewer 1 to explain how did I demerit other models?

I hope you will read my response to the reviewers' comments and decide yourself based on the merit of my response.

In the discussion section I cited the following:
According to George Box, "Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration. On the contrary following William of Occam he should seek an economical description of natural phenomena (105). I came across this statement few years ago and believed it and started looking for simple models and after several years of work I have become a strong believer in the statement of George Box.
In Fact, Box further added that: Just as the ability to devise simple but evocative models is the signature of the great scientist so over-elaboration and over-parameterization is often the mark of mediocrity." (I did not include this part in the manuscript).

Recently, I came across the following comment and I have now included this in my manuscript (reference 106) along with George Box. In a recent article, Deyme et al highlighted the usefulness and practical values of simple models. The authors wrote "Conversely, such simple models are the most likely to reach bedside application because of their simplicity. It is critical to balance the pros and cons of each strategy for precision medicine in real-world settings. Models should rather be built in the perspective of future practical application. Indeed, for an efficient in silico-to-bedside transposition, we believe that the more complex is a phenomenon, the simpler should be the mathematical model describing it".
Deyme L, Benzekry S, Ciccolini J. Mechanistic models for hematological toxicities: Small is beautiful. CPT Pharmacometrics Syst Pharmacol. 2021;10:396-98.

Reviewer #1:

Please differentiate oral and IV doses in the data. Authors failed to discuss role of bioavailability and focused predominantly on clearance.

In Table 1, I have already identified about oral and IV administration. I did not fail to discuss the role of bioavailability since it has nothing to do with this work. Indeed, the focus was on clearance (CL) because one of the objectives was to predict clearance and subsequently predict dose (method 3) discussed in the manuscript. Bioavailabilty is not the focus here. The CL following oral administration is CL/F where F is bioavailability and is taken into account in the equation and for CL values.

Authors discussed and suitably estimated/chosen exponents for clearance and BW based methods. This is expected to improve the performance of the data on which the estimate of exponent was chosen for.

I highly encourage the authors to have independent test set.

It seems to me that there is some misunderstanding about the methodology. In this study, I did

not develop any model for the drugs I used for my analysis rather these are published models and references were provided in the manuscript for every model or method.

Method 1: Several years ago (reference 2 was published in 2014 and has the description of this model), I developed this method as a compromise between exponent 0.75 and 1.0 because these two exponents were not found suitable across all ages (references 2, 8, 9, 83). Exponent 0.75 and 1.0 are well known allometric exponents for the prediction of clearance and dose (reference 2) and are in existence since decades. In fact, exponent 1.0 is used for dose prediction in children directly extrapolated from adult dose (per kg body weight basis) and is very well known. In this study, I used exponent 0.9 for dose prediction based on previous analysis not using the data from this study.

Method 2: Salisbury Rule was developed by Lack and Stuart in 1997 (reference 10). They developed the model based on their data and I simply used their equations 3 and 4 for my analysis (validation of their method on the drugs I used in my analysis). It is clearly written that "This method was proposed by Lack and Stuart-Taylor and is as follows (10)". Lack and Stuart-Taylor had already validated their method and found the method's predictive power acceptable (10).

Method 3: I developed this model called Age Dependent Exponent (ADE) model several years ago and the model was previously used for the prediction of clearance across the age groups including preterm neonates (references 2, 8, 88-91). This method was also described in reference 2 published in 2014.

As mentioned above, I used previously developed models and used these models for the prediction of clearance or dose in this study. The purpose was to compare the Salisbury Rule with other methods. Salisbury Rule is very simple and I find no reason not to explore it and compare it with other methods including well known empirical model PBPK. All models used in this study were for prediction purposes because these models were previously developed and were not developed in this study or data from this study.

Authors should at least attempt to understand the clearance mechanisms especially if drugs are predominantly really cleared or metabolized before attempting to compare such wide range of methods. It will help to know how different method worked for renally cleared vs metabolically cleared drugs.

How did the reviewer come to the conclusion that I do not understand the clearance mechanism and should try to understand? I fully and very well understand the clearance mechanism. The allometric exponents described here work equally well for both extensively renal or extensively metabolized drugs (References 8-9, 88-91).

Having simple exponent fitting may appear good statistically especially when applied on the same data where exponent was identified or fitted. Pediatric dose estimation was as easy as changing exponent from 0.75 to 0.9, this complex research topic would have been solved decaded ago. I would appreciate if authors can give due credit to scientific complexity involved in such research area than to simplify the conclusion to simple change in exponent solving the issue.

As I mentioned earlier, the exponents or models were not developed from the data in this study rather previously developed models were used. I explained in the text for using exponent 0.9 which I developed few years ago. I do not know what is the scientific complexity here? It is a very simple issue. Exponent 0.75 does not work in young children (generally <2 years especially, preterm and term neonates) for dose and clearance prediction known at least since three decades. Previously, I used exponent 0.9 as a compromise between 0.75 and 1.0 and this worked very well. These are empirical models and are not complex. Several years ago, I developed exponent 0.9 for dose prediction and the ADE model for the prediction of clearance. There is no complexity here. I have given the references and interested reader can go to these manuscripts and read.

PBPK models are based on scientific knowledge we have on maturation of human body, enzymes and other physiological processes. Scientifically there are many gaps in our knowledge hence it is conceivable PBPK may not resolve the challenges of pediatric dose finding especially neonatal. However, I have strong reservations on the conclusions authors have drawn about PBPK vs simpler methods based on limited research methodology they have employed. In all simpler approaches, authors fitted or fudged exponent or other parameters of the model to make the predictions look good on the same data for which it was fitted. On the other hand, PBPK models were gathered from literature and in many cases the purpose of those models was not pediatric dose finding. If authors want to do scientific comparison, they need well-defined modelling data set and their own PBPK model building or choosing suitable cases from literature. With such limited and biased methodology, I would strongly recommend the authors conclude suitably without demeriting any of the approach. Authors need more independent testing of approaches on independent data set to make meaningful conclusion on comparisons.

All models are empirical models including PBPK and are based on scientific knowledge including simple models as described here. The models used here to compare with the PBPK models were developed previously and are validated models from external data. New methods (simple or complex) have to be developed and compare with the existing or established methods and I exactly did this. New thinking and new methods have to go on in research and discovery.

The reviewer's statement "In all simpler approaches, authors fitted or fudged exponent or other parameters of the model to make the predictions look good on the same data for which it was fitted".

This statement is entirely incorrect. Nothing was fitted or fudged here or done to look prediction good. This is a baseless accusation because the reviewer simply did not understand the methodology and did not look at the references provided for these models. I have already explained the methodology earlier and hope he/she will understand what was done here.

The reviewer states "PBPK models were gathered from literature and in many cases the purpose of those models was not pediatric dose finding".

I will suggest that the reviewer look at the references (62, 64, 67, 69, 70, 72, 80, 83, 86, 87). Ten out of 11 PBPK studies used in this analysis indicate in their title that the dose projection is the objective of the PBPK modeling (references provided above). In other words, just looking at the title of the study one can very easily figure out that the objective of these studies were dose finding. Reference 76 although, does not indicate that it is a dose finding

study but looking at the study one can easily find out the objective is dose finding. I would like to know from the reviewer if dose projection was not the objective of these authors then what was their purpose of doing PBPK modeling and how did the reviewer come to the conclusion that the purpose of these PBPK models were not dose finding?

I am not a PBPK modeler but I have a very clear understanding of the concept of PBPK model. The methodology I used are not biased. They were previously developed and used in this study for the assessment of the predictive power of the Salisbury Rule and compare it with other models. The cases of PBPK I chose from the literature are well defined PBPK models (as I see it). Somehow, I believe that this reviewer thinks that PBPK models should work better than all other models. If it does not then all comparative studies are incorrect because a right kind of PBPK model was not chosen for comparative purpose or the models developed to compare with PBPK are incorrect and made up. I would like to know from the reviewer why the PBPK studies I chose from the literature are not suitable for the comparison purpose? Please identify the shortcomings of these studies from PBPK perspective.

My conclusions are based on the data analysis and the performance of the models. All models were validated in previous studies with external data and in this study these models were used to validate the predictive performance of Salisbury Rule and then compare it with other models developed previously including PBPK. The conclusion is based on the data analysis and quite suitable for the objectives of the study. The sample size (27 drugs and 113 observations) is large enough to draw conclusions.

Please highlight my statements in this study which **demerit** other approaches.

If the reviewer provides me with compelling evidence about his/her comments that the purpose of the PBPK modeling which I used for comparison with other models was not dose projection and the PBPK models are erratic or deficient (all 11 PBPK studies I used in the comparison) and are not suitable for comparison purpose, I will remove PBPK from comparison.

Some technical comments:
Language is difficult to follow, please have a English language-proofing.
I come from a English speaking country and I know 'English language' very well.

Line 54 - It should be equation 4.
Agree. I have corrected it.

Equation 5 - what is the rationale for applying exponent again when it was already applied to clearance in equation 4. Authors should provde biological or scientific explanantion than to find exponents that may fit the data they are seeing. Otherwise validate the equation on independent data set.

Equation 5 is for dose and equation 4 is for CL prediction. These are different exponents for different purposes. All models were developed in previous studies and validated.

Lines 56-59 - Please cite and read original references than to base your work on indirect references, at least when citing the method by name.

I have no understanding of this comment. What is original or indirect reference? How will I read original references in a manuscript? References cited here are based on the original work of the authors. Please provide an example.

Reviewer #2.

I thank you for writing some very good important general comments on my manuscript and here is my response. I have parsed your comments to respond directly.

With pleasure I have read your manuscript. I believe it is of high value to compare different approaches to derive dosing regimen to our vulnerable pediatric population.

Thank you for your encouraging comment.

Allometry or other simple approaches that are using allometry has it's pro's and con's versus mechanistic models such as PBPK models (which btw are not empirical/data driven models which you are stating).

I hope you are not implying that PBPK or other mechanistic models has no pros and cons. I wrote at the end of the discussion section the following:
According to George Box, "Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration. On the contrary following William of Occam he should seek an economical description of natural phenomena (105).

This is a very strong statement and I fully agree with this. This concept of George Box led me to think and develop simple models which have good predictive power.

All models have pros and cons whether a model is as simple as allometry or complex like a PBPK or a pharmacometric model. All models are data driven including the mechanistic models such as PBPK and pharmacometric models. I have nothing against PBPK or any other model. I consider models useful and of practical value. Like all other models, PBPK is erratic and with uncertainty about its predictive performance. The acceptable prediction error is 0.5-2-fold. In other words, if the prediction error is <2-fold then the model's performance is good. I disagree with this magnitude of error for any practical purpose in a biological system.

The name "physiological-based pharmacokinetic model" (PBPK) has created a false impression among people that PBPK is really a physiological model. PBPK is indeed an empirical model and is data driven. The model uses mean physiological values from whole body called whole body 'PBPK' (it is now well known that whole body PBPK is unnecessary and few physiological parameters do the job as good as whole body physiological model) (references 93-99). PBPK model requires values from PK such as clearance and volume of distribution, drug properties such as pH, pKa, partition coefficient, protein binding and many other parameters depending upon a modeler's understanding and assumption of the model. Are PK parameters and other essentials of PBPK model not data driven? Indeed, these are. The question is whether a model needs to be mechanistic or physiological and not data driven? In my mind the answer is 'NO'.

Let us face a grim fact that we do not know even 5% of the physiological process which goes on in a multi-cellular organism such as humans and animals. Thinking that using few physiological parameters and some characteristics of drugs as I mentioned above and some

PK parameters the model is in true sense physiological does not make any sense. This is the reason that many clinical pharmacologist including myself, and even some real knowledgeable PBPK modelers consider PBPK an empirical model. There is nothing wrong for a model to be empirical as long as it provides desired results. Allometry is empirical but its predictive performance for pediatric dose or clearance is as good a PBPK model (reference 83, 88, 97, 100, 101).
However, methodologically it seems that the methods you have applied (such as the usage of a 0.9 exponent) seem more to be data driven rather than having a physiological meaning, using too few drugs to really make a statement.

All models are data driven including PBPK. One can not build a model without data. It is also not necessary for a model to be physiological. I have shown that for clearance and dose that allometry is as predictive as PBPK models (References 83, 88, 97, 100, 101). I used 27 drugs and there are 113 observations (different age groups) to show my comparison. How many drugs and observations one needs to prove a point? One does not always need a model with physiology as shown in this paper and several other papers I have referenced.

Depending on the included drug with its pk characteristics, the result may be completely different. Additionally, instead of retrospective comparison of actual data, the resulting doses are compared, and mean clearance values.

I have no understanding of the statement. Regarding model development I have the following comments:

Method 1: Several years ago (reference 2 was published in 2014 and has the description of this model). I developed this method as a compromise between exponent 0.75 and 1.0 because these two exponents were not found suitable across all ages (references 2, 8, 9, 83). Exponent 0.75 and 1.0 are well known allometric exponents for the prediction of clearance and dose (reference 2) and are in existence since decades. In fact, exponent 1.0 is used for dose prediction in children directly extrapolated from adult dose (per kg body weight basis) and is very well known. In this study, I used exponent 0.9 for dose prediction based on previous analysis not using the data from this study.

Method 2: Salisbury Rule was developed by Lack and Stuart in 1997 (reference 10). They developed the model based on their data and I simply used their equations 3 and 4 for my analysis (validation of their method on the drugs I used in my analysis). It is clearly written that "This method was proposed by Lack and Stuart-Taylor and is as follows (10)". Lack and Stuart-Taylor had already validated their method and found the method's predictive power acceptable (10).

Method 3: I developed this model called Age Dependent Exponent (ADE) model several years ago and the model was previously used for the prediction of clearance across the age groups including preterm neonates (references 2, 8, 88-91). This method was also described in reference 2 published in 2014.

As mentioned above, I used previously developed models and used these models for the prediction of clearance or dose in this study. The purpose was to compare the Salisbury Rule with other methods. Salisbury Rule is very simple and I find no reason not to explore it and compare it with other methods including well known empirical model PBPK. All models used in this study were for prediction purposes because these models were previously

developed and were not developed in this study or data from this study. The predicted doses were compared with the actual dose. It is clearly written on page 5 just above method 2 that "The predicted dose was compared with the observed dose. The observed dose(s) were obtained (depending upon the availability) from the package inserts of the FDA, Drugs.com and also from the studies in which children of certain age were given certain doses.

Also, there are other papers out there clearly showing the opposite statement that allometry does not work. As you have also shown in your manuscript, especially in the newborn, where maturation of active processes, and rapid changes of body composition occurs, simple allometry does not properly predict exposure in children.

I exactly do not know what do you mean by saying that allometry does not work and it has been clearly shown. I believe that you mean to say that allometry does not work in younger children like preterm and term neonates for clearance or dose prediction. This is in fact, incorrect view. Please provide me with some references which clearly show that allometry does not work. This should be based on by data analysis and not by theoretical thinking. I have shown in this paper and in dozens of my papers that allometry works and works very well and comparable with other models especially, PBPK (references 83, 88-90, 97, 101, 103).

Allometry does work very well even in preterm neonates (reference 83, 88-91, 101, 103). Allometry is not defined by theoretical exponent 0.75 for clearance and 1.0 for volume of distribution. Allometry is not based on fixed exponents or has any universal exponent(s). Allometric exponents widely vary and are data dependent (102). Exponent 0.75 introduces substantial prediction error in clearance and dose prediction in preterm and term neonates and children under two years of age. In order to fix this, I introduced Age independent exponent (ADE) and it works right from preterm neonates to adolescents. This method was validated in my many papers and was used to predict clearance of drugs used in this study (References 83, 88-91, 101).

What I also agree from your introduction, that pathophysiology may also completely differ from that of adults which is another aspect that one would need to consider, that is lacking when applying these simple methods. For this reason, I was not convinced that with the few drugs being selected for testing, simple methods would suffice or be equally well predicting for First in pediatric doses selection.

The thinking is correct that pathophysiology of children completely differ from that of adults. The theory is conceptually correct but in a real world empirical models are good enough to obtain a desirable result as shown in this study and many other studies (references 83, 88-91, 97, 100-101). This does not mean that only a model with inclusion of some physiological parameters all in a sudden will give the best results or is the best model. There are pharmacometric models as well as pure allometry based models that work very well without incorporation of physiological parameters (83-92, 97 101).

You need to look at the data. In other words, what is the analysis and what is the outcome? Does the analysis say that the results are not comparable with the observed values? There are 27 drugs and 113 observations. This is not a small sample size. The analysis points out a

single direction that is the predicted values are comparable with the observed values for most of the observations. If the prediction would have been mixed that is that few drugs were predicted well and few drugs poorly then one can question the sample size and the predictive power of the model(s).

All models are empirical including PBPK as I explained earlier. There are 11 drugs and 26 observations where PBPK projected dose were compared with other methods and all point in the same direction (comparable). How many drugs one needs to prove a point? I have already mentioned in the text that there are not many PBPK models that attempt to predict dose in pediatrics.

Bottom line is that PBPK model like any other empirical model is error prone and with uncertainty. This is perfectly alright because there is no perfect model but the PBPK model does the desired job with fair degree of accuracy. PBPK model by no means is superior than any other model and there is no reason for not looking and searching for other models whether the model is simple or complex. This can be only found out by research and comparative studies not just by sitting in a black box world doing the same thing again and again thinking that this is the best thing in the universe which I am doing.

Reviewer #3:

1. Does adult dose come from FDA labels? The observed dose of pediatrics seems to have multiple sources, so how to determine which source of data to choose for statistical analysis in this study?

I mentioned under methods section:
"The proposed actual doses of these drugs were obtained from the FDA package insert, Drugs.com, and from the studies where a particular dose was given to an age group".
FDA package insert not necessarily provided pediatric dose for each and every drug but adult dose was available. If Drugs. com or FDA label did not have pediatric dose then the pediatric dose was based on the published study in a manuscript. For pediatric dose, the first choice was FDA labeling, second choice was the literature and the third was Drugs.com. The fact is that pediatric recommended dose by these three sources were very much similar. Many recommended pediatric dose in the FDA labeling came from the literature.

2. Although PBPK models were obtained from literature, but what kind of computer software was used for data calculation when using of PBPK models in this study, was it the same with the obtained literature?

The PBPK model used in this study was literature-based and I did not develop any PBPK model myself.

3. On page 4, the two formulas in method 2A were not clear.

I do not know how to clarify it? The method is clear to me.

4. There were other pediatric dosing rules such as Clark's Rule (2-17 years), Clark's Surface Area rule, Young's rule, Webster's rule, Fried's Rule, and Shirkey's BSA Recommendation, although some studies have shown that they might be unreliable, now that they had been

published and used, why comparing the rules with the four methods in this article to see if there is a big difference.

Initially, I thought to analyze these methods. Then I realized that the work has already been done and there will be also too many methods in this manuscript and will be difficult to grasp. When I was in the FDA, we did an internal study with 76 drugs and found that these methods were indeed poor for pediatric dose prediction. Less than 50% drugs reached to the observed values with an accepted 30% prediction error (unpublished data).

5. How many observed dose(s) of pediatrics were from the FDA labels? For labels with both adult dose and pediatric dose, which rule gives a better prediction?

I do not know because no such analysis was done. In many cases, the FDA labeling for pediatrics cited the dose and PK parameters from published literature rather than sponsor-based studies.

6.What was the source of 113 observations across the age groups? Was there multiple data sources for a same drug? If there were multiple observations for a same drug, and the differences between each observation were small, the reliability of statistical results of this study will be seriously affected. In other words, multiple approximate data for a same drug may affect the percent prediction error result.

There were 27 drugs and 113 observations in this study. The 113 observations are because a drug may have several age groups. The observed and predicted dose and CL differ from one age group to the other. There was only one observation (CL or dose) for a given age group.

7. The author needs to further explain the sources of the data in the paper.

I do not know how? I have already provided the references for drugs and the models.

8. Do not see the percent prediction error of the whole body PBPK rule?

I only used the predicted dose from the PBPK model. I ignored the prediction error from PBPK model because the objective was to compare the predicted values across all models including PBPK.

2nd Editorial decision
18-Aug-2022

Ref.: Ms. No. JCTRes-D-22-00087R1
A Comparison of Different Methods for the First-in-Pediatric Dose Selection
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Journal of Clinical and Translational Research
Peer review process file 08.202205.003

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: