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Prediction of total and renal clearance of renally secreted drugs in neonates and infants (≤3 months of age)

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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 30, 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:

Reviewer #2: I have read your manuscript, please consider a native englisch writer to improve the wording of the manuscript. Although a very interesting comparison between very simple mathematical model versus a more physiology-based model, the conclusions that you draw for a first dose in children to be only based on a clearance prediction is very misleading, as other adme properties can also play a strong role in the dose decision making. Generally I would also recommend on focusing and discussing more on the safety and efficacy of a drug in children, and the possible differences in disease indication that may also be needed to be incorporated in such models before doing predictions. All these factors can impact the dose that would be needed. Below you can find my comments and further suggestions:

abstract:
- correct clearanceclearance typo

page 2:
- rows 7-8: what is the difference between metabolism and renal route in your opinion? There are different metabolic pathways and also other forms of non-renal elimination (e.g. biliary clearance, endosomal clearance). please reconsider your wording.
- row 10: some processes may be linear (cyp3a5 is known not to change after birth. Please consider using 'most' changes rather then generalising it to all age-related changes.
- row 13: consider using healthy adults, especially when i come to prediction of pk, the health state (GFR decrease) can play a significant role.
- 17-19: this is a wrongly written sentence, I would recommend a professional english writer to improve the textual content of the manuscript.
- row 20: does this mean that a protein bound substance can be excreted renally via transporters? Indirectly tubular secretion would be dependent on plasma protein binding.
- row 22-23: I would disagree with this general statement of maturation time. Tubular secretion of a substance is completely dependent on the transporter(s) involved and with that the maturation of the transporter(s), which can vary significantly.

page 4:
- row 34-35: A 2 fold error is a generally accepted and widely used error range, could you explain the reason why not to accept this for any particle purpose?

page 5:
- section renal clearance: please inform on which other routes of elimination are there for each drug that you used as example. Again, protein binding can play a major role in the elimination of a drug that is systemically available.
- row 58-59: see my comment on the same sentence in row 20 of the introduction on page 2

page 6:
-row 6-7: see my comment on the same sentence in the introduction in page 2.
-row 12-14: please be more specific: active processes ? GFR? for sure not all processes are

shown to be nonlinear, and some processes are already mature such as CYP2J2 and CYP3A5 activity.
-row 16-17: before you considered allometric models not to be physiological, and the two minimal models physiological.....I am confused?
row 34-35: this clearly depends on what the purpose is of the modeling, please reword, that you mean this in the context of predicting renal clearance only, not taking into account other ADME properties that can have significant impact on e.g. Cmax or Ctrough and with that Safety and/or efficacy of a drug dose. A simple model would never be able to provide this information.
row 40-43: Please read literature more carefully before making such hard misleading statements. (whole-body) PBPK is the closest one can get to real physiology (in vivo) and ideal to extrapolate to special populations such as neonates, other formulations, and possible different dosing outcomes. It has shown to provide very accurate predictions compared to in vivo clinical data. I would recomment rewording.

page 7:
lines 4-6 : please specify for which purpose this was tested. see my previous comments
lines: 23-26: predicting clearance cannot always be directly correlated to the dose that children need in clinical practice, other ADME properties and types of formulations can be highly variable and different in newborns and needs to be considered, for which whole-body pbpk models are ideal to use. I recommend to include this information.
line 30:32: there are pbpk modeling software out there that are definitely not based on experience but on peer reviewed original research outcome, and are user-friendly that everyone with some physiological knowledge can easily use. I completely disagree with such a strong and demeaning statement. I strongly consider rewording this sentence.

Reviewer #3: 1. What is the age means in the tables? The author should pay attention to distinguish gestational age, chronological age, postnatal age?
2. How were the 12 drugs selected? There are other drugs with high renal clearance rate, such as meropenem, imipenem and azithromycin.
3. For "An acceptable prediction error in the literature is 2-fold", the references should be provided.
4. If the racial differences should be considered ?

Authors' response

Reviewers' comments

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Clearance (CL) is based on exposure (Dose/AUC) and this parameter incorporates concentrations in the systemic circulation of a drug which has already gone through the process of ADME. I am not the first person who has used CL for dose prediction rather thousands of clinical pharmacologists use CL for dose prediction and is widely used and accepted. This approach was found to be very useful and accurate for dose prediction both in adults and children. Therefore, I am not misleading anybody and the concept is correct and not new.

abstract:
- correct clearanceclearance typo

There is no typo in abstract on page #1.

page 2:
- rows 7-8: what is the difference between metabolism and renal route in your opinion? There are different metabolic pathways and also other forms of non-renal elimination (e.g. biliary clearance, endosomal clearance). please reconsider your wording.

Not only in my opinion but also in the opinions of thousands of clinical pharmacologists, pharmacologists, physiologists, biochemists, and medicinal chemists (and many more from other biologic disciplines) that metabolism means when a drug is metabolized by liver or gut enzymes or some metabolic enzymes found in other organs of the body. Renal route is generally refers to any substance (can be a drug or the metabolite of a drug) which is excreted by renal route (means excretion in the urine). This paper only deals with drugs which are renally secreted (means drugs are extensively eliminated by the renal route). Metabolic and non-renal clearances are irrelevant to this study and there is no need to mention about these. Therefore, my statement is correct and there is no need to discuss metabolic and non-renal clearance.

- row 10: some processes may be linear (cyp3a5 is known not to change after birth. Please consider using 'most' changes rather then generalising it to all age-related changes.

Metabolic process or changes have nothing to do with this paper. My statement is regarding the renal clearance.

- row 13: consider using healthy adults, especially when i come to prediction of pk, the health state (GFR decrease) can play a significant role.

The GFR in healthy adults is 120 mL/hr hence, the statement is regarding healthy subjects. I used the total and renal clearance of healthy adults in the analysis. I have now mentioned this in the method section.

- 17-19: this is a wrongly written sentence, I would recommend a professional english writer to improve the textual content of the manuscript.

Please tell me what is wrong in these two sentences (both from English and scientific perspective).

- row 20: does this mean that a protein bound substance can be excreted renally via transporters? Indirectly tubular secretion would be dependent on plasma protein binding.

Tubular secretion does not depend on plasma protein binding rather it is entirely dependent on renal blood flow (please see reference 3 & 4 in this manuscript). Protein binding is an obsolete concept. Please see the manuscript entitled: " Benet LZ, Hoener B-A. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Therp. 2002,71:115-121. This manuscript was published 20 years ago. Amazingly, some people still think that protein binding is important.

- row 22-23: I would disagree with this general statement of maturation time. Tubular secretion of a substance is completely dependent on the transporter(s) involved and with that the maturation of the transporter(s), which can vary significantly.

Tubular secretion is not completely dependent on the transporter(s). It is mainly dependent on renal blood flow. In my manuscript I wrote that " Tubular secretion is an active transport process and is independent of plasma protein binding but dependent on renal blood flow (4). Drug secretion also depends on the affinity of the drug for carrier proteins in the proximal tubule, the rate of transport across the tubular membrane, and the rate of delivery of the drug to the site of secretion (4). Tubular secretion is immature at birth and approaches adult values by 7 months of age (4). This statement is correct. Please see references 3 & 4.

page 4:
- row 34-35: A 2 fold error is a generally accepted and widely used error range, could you explain the reason why not to accept this for any particle purpose?

I know 2-fold prediction error is widely used by modelers especially, PBPK modelers. The modelers use this wide range of prediction error to mask their substantial prediction error. You do not want to project a dose or a PK parameter in adults or children with 99% or even 80% prediction error (all these errors are within 2-fold) and claim that the prediction is accurate. These prediction errors are too high for dosing or for the estimation of PK parameters. After I hammered on this wide range prediction error the trend is now shifting to 0.5-1.5-fold error, which I think is still too high.

page 5:
- section renal clearance: please inform on which other routes of elimination are there for each drug that you used as example. Again, protein binding can play a major role in the elimination of a drug that is systemically available.

Route of elimination for all drugs used in this study are related to renal secretion (means renally excreted drugs). Tubular secretion has nothing to do with protein binding.

- row 58-59: see my comment on the same sentence in row 20 of the introduction on page 2. I have already responded to your comments.

page 6:
-row 6-7: see my comment on the same sentence in the introduction in page 2.
I have already responded to your comments.

-row 12-14: please be more specific: active processes ? GFR? for sure not all processes are shown to be nonlinear, and some processes are already mature such as CYP2J2 and CYP3A5 activity.

This entire paper is about renal secretion and I am only talking about renally secreted drugs.

-row 16-17: before you considered allometric models not to be physiological, and the two minimal models physiological.....I am confused?

Allometric models are not considered physiological models and the other two models carry physiological parameters in terms of kidney weight and kidney blood flow and GFR hence, these are physiological models. It is not necessary that a physiological model should have all the body organs. It has been shown that minimum physiological model works as good as whole body PBPK model (References 12, 24-29).

row 34-35: this clearly depends on what the purpose is of the modeling, please reword, that you mean this in the context of predicting renal clearance only, not taking into account other ADME properties that can have significant impact on e.g. Cmax or Ctrough and with that Safety and/or efficacy of a drug dose. A simple model would never be able to provide this information.

Your assertion that "A simple model would never be able to provide this information" is not correct. Please see references 12, 16, and 24-29. Both renal and metabolic clearances can be predicted accurately by simple models and are comparable with the whole body PBPK. This manuscript predicts both total and renal clearance and the results do show that the predicted values are comparable with the observed values. Hence, you do not need to go very far. Just look at this manuscript and you will find that a simple allometruc model and two very simple physiological models provided accurate prediction of total and renal CL in the neonates. The prediction error remains <40% which is far less than your acceptable prediction error of 2-fold. This is only for neonates. In older children, the prediction of total and renal CL will be even more accurate. In fact, here is a research project for you. You can compare the three proposed methods with your whole body PBPK and let us see what do you get?

row 40-43: Please read literature more carefully before making such hard misleading statements. (whole-body) PBPK is the closest one can get to real physiology (in vivo) and ideal to extrapolate to special populations such as neonates, other formulations, and possible different dosing outcomes. It has shown to provide very accurate predictions compared to in vivo clinical data. I would recomment rewording.

I am very well familiar with PBPK literature and what I wrote is correct based on data analysis and research. The works of many investigators has clearly shown that a reduced PBPK model provides similar results as a whole body PBPK model (references 24-29). What is the definition of accurate prediction? Within 2-fold prediction error? This is not accuracy. I agree that whole body PBPK is closest to real physiology but as they say 'buck stops there'. You have not created a living organism. we hardly know the physiological processes in a living organism. The reduced PBPK models clearly show that whole body PBPK is unnecessary. One should not forget that PBPK is an empirical model and has very little to do with the reality of physiology and physiological processes of a living organism. In fact, the

name PBPK model is misleading rather it should be called "Physiology-based empirical model'.

page 7:
lines 4-6 : please specify for which purpose this was tested. see my previous comments

The purpose or objective is very clearly written in the manuscript. It reads that Mahmood and coauthors have **compared** minimal physiological or allometric models with whole body PBPK model. It was basically a comparative study between whole body PBPK and minimal PBPK and allometry. The results of the study showed that the minimal PBPK or allometry provided similar results as whole body PBPK.

lines: 23-26: predicting clearance cannot always be directly correlated to the dose that children need in clinical practice, other ADME properties and types of formulations can be highly variable and different in newborns and needs to be considered, for which whole-body pbpk models are ideal to use. I recommend to include this information.

Your statement is not correct.
Clearance (CL) is based on exposure (Dose/AUC) and this parameter incorporates concentrations in the systemic circulation of a drug which has already gone through the process of ADME. I am not the first person who has used CL for dose prediction rather thousands of clinical pharmacologists use CL for dose prediction and is widely used and accepted and provide accurate results. This approach was found to be very useful for dose prediction both in adults and children. Whole body PBPK model may be ideal but there are other simple models which are equally good and robust in their predictive performance as whole body PBPK (references 6-8, 12, 15-16, 24-29). Besides these references, there are many other papers which show that whole body PBPK is unnecessary and provides no advantage over simple models or reduced PBPK models.

line 30:32: there are pbpk modeling software out there that are definitely not based on experience but on peer reviewed original research outcome, and are user-friendly that everyone with some physiological knowledge can easily use. I completely disagree with such a strong and demeaning statement. I strongly consider rewording this sentence.

You may disagree but my statement is scientifically and logically correct. Please provide evidence that my statement is demeaning. I will soften the language.
The problem lies with 'some knowledge'. 'Some' knowledge of physiology, pharmacology, medicinal chemistry, biochemistry, and PK is not good enough even for a PBPK modeler.

Reviewer #3:

1. What is the age means in the tables? The author should pay attention to distinguish gestational age, chronological age, postnatal age?

Chronological age. Now mentioned in the Table.

2. How were the 12 drugs selected? There are other drugs with high renal clearance rate, such as meropenem, imipenem and azithromycin.

The selection criteria was that the drugs should be renally secreted in the adults and the CL data are available for both adults and the neonates. I have now added the selection criteria in the method section (in red).

Meropenem is renally secreted but I refrained from using meropenem in my analysis mainly due to substantial differences in the CL values for adults and neonates observed in the literature. For example, the reported adult total and renal CL values were 186 mL/min/m^2 and 142 mL/min/m^2 respectively (Christensson BA et al (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1992, p. 1532-37), 328 mL/min/m^2 and 252 mL/min/m^2 respectively (Leroy A et al (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1992, p. 2794-98), and 203 mL/min/m^2 and 137 mL/min/m^2 respectively, (Ljunberg B et al (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1992, p. 1437-40).

For preterm neonate the CL value was 0.157 L/kg/hr (van Enk JG et al, Therapeutic Drug, Monitoring, 2001 **23:**198–201). A manuscript by van den Anker JN et al (ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2009, 3871–79) provides equation (equation 1) to calculate clearance. My attempt to calculate CL from equation 1 for preterm neonates using mean body weight and mean creatinine CL ended in a negative CL value. For term neonates the CL value was positive. Therefore, due this kind of discrepancy, I avoided meropenem.

Imipenem is not renally secreted and azithromycin is mainly biliary excreted.

3. For "An acceptable prediction error in the literature is 2-fold", the references should be provided.

It is difficult to provide a particular reference because in the modeling community this is a common trend. Two references are as follows:
Yun YE , Edginton AN. Model qualification of the PK-Sim® pediatric module for pediatric exposure assessment of CYP450 metabolized compounds. J Toxicol Environ Health A. 2019;82(14):789-814.
From the abstract: Eighty-one percent of the comparisons between simulated and observed clearance values were within twofold error.

Zhou et al. Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children. Clin Pharmacol Ther 2018 Jul;104(1):188-200.

From the abstract: Collectively, 58 out of 67 predictions were within 2-fold and 43 out of 67 predictions within 1.5-fold of observed values.

I do not know the origin of the 2-fold error concept but my guess is that it was first presented by pharmacometricians and later PBPK modelers adopted it. I believe that this 2-fold acceptance criteria is too wide and basically masks the predictive error of a model. In a biological system, such a large predictive error should not be acceptable. I pushed for 0.5-1.5-fold error and it is now in use but I think that even this magnitude of error is too wide and in this study, I used a 30% prediction error.

4. If the racial differences should be considered ?

Racial differences should be considered but this is my theoretical view. I think that at the moment, there are not enough data which can establish racial differences in the neonates for drugs which are renally secreted.

Yejin Esther Yun , Andrea N Edginton. Model qualification of the PK-Sim® pediatric module for pediatric exposure assessment of CYP450 metabolized compounds. J Toxicol Environ Health A. 2019;82(14):789-814.
From the abstract: Eighty-one percent of the comparisons between simulated and observed clearance values were within twofold error

Zhou et al. Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children. Clin Pharmacol Ther 2018 Jul;104(1):188-200.

From the abstract: Collectively, 58 out of 67 predictions were within 2-fold and 43 out of 67 predictions within 1.5-fold of observed values.

Renal Insufficiency
Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of
azithromycin (4 × 250 mg capsules), the mean Cmax and AUC0-120 increased by 5.1% and 4.2%,
respectively in subjects with GFR 10 to 80 mL/min compared to subjects with normal renal function (GFR >80 mL/min). The mean Cmax and AUC0-120 increased 61% and 35%, respectively in subjects with end-stage renal disease (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Azithromycin is primarily excreted unchanged via the biliary tract and subsequently eliminated in stool, with very little excretion occurring via the kidneys.

Intravenous Azithromycin
Kevin W Garey and Guy W Amsden
Ann Pharmacother 1999;33:218-28.

2nd Editorial decision
09-Sep-2022

Ref.: Ms. No. JCTRes-D-22-00086R1
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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.

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: