

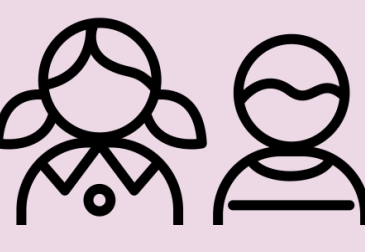
Comparison of Body Weight and Body Surface Area-Based Dosing in Paediatric Population using PBPK modelling

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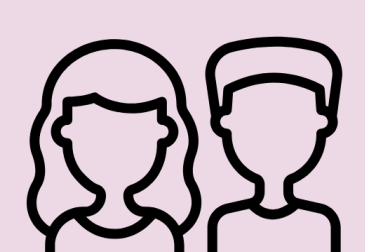
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Introduction

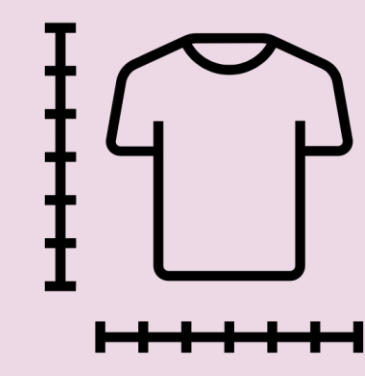
Paediatric dose optimization



vs



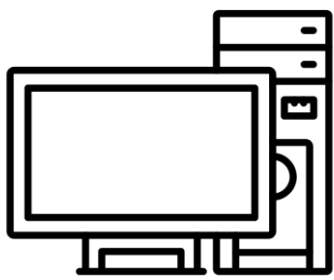
Given the variability in children's weights, dosing is often adjusted using **Body Weight (BWT)** or **Body Surface Area (BSA)** methods.



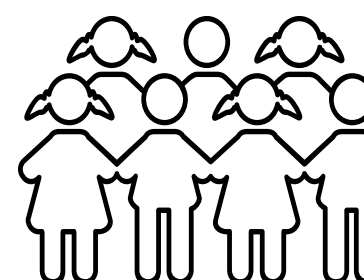
However, the ideal approach is not well-defined, and it's unclear whether BWT and BSA dosing strategies result in comparable drug exposure, making their interchangeability questionable.

This study hypothesizes that BWT and BSA dosing result in similar drug exposure in children but may yield different outcomes in children with extreme percentile weights.

Methods



Model validation in Simcyp, Certara (v23.2)



Simulation of 5.000 paediatric subjects

50% ♀

50% ♂

6 – 12 years

Model validation was using the following paediatric clinical studies:

- Azithromycin: Nahatta et al. 1993
- Raltegravir: Meyers et al. 2019, Nachman et al. 2014
- Itraconazole: Schmitt et al. 2011, Groll et al. 2002

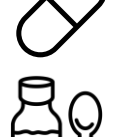
The absolute average fold error (AAFE) was: 1.19, 1.14, and 1.36-fold for azithromycin, raltegravir, and itraconazole paediatric models, respectively.

BSA was calculated using the du Bois formula and BSA dose was calculated as follows:

$$BSA \text{ (mg/m}^2\text{)} = W^{0.425} \times H^{0.725} \times 71.84$$
$$BSA \text{ dose (mg/m}^2\text{)} = \frac{\text{Average BWT (28 kg)} \times \text{BWT dose (mg/kg)}}{\text{Average BSA (1.02 m}^2\text{)}}$$



Azithromycin oral solution



Raltegravir chewable tablet



Itraconazole oral solution

The resulting doses were:

	BWT based dose (mg/kg)	BSA based dose (mg/m ²)
Azithromycin	5	146
Raltegravir	12	330
Itraconazole	2.5	69.1

Children were categorized according to Body Mass Index (BMI) percentiles accounting for age into:



<5th



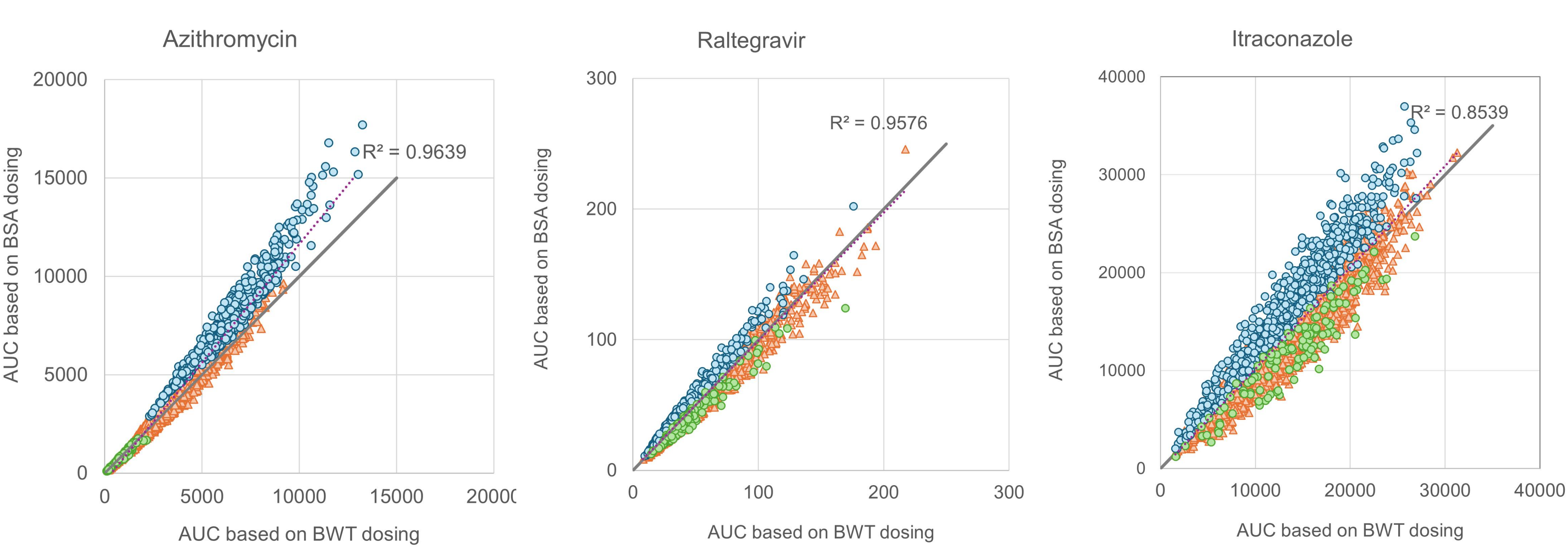
Median (5th-95th)



>95th

- Area Under the Curve (AUC) comparability was assessed using the ratio of AUC derived from BSA-based dosing to that from BWT-based dosing.
- Equivalence was defined by an AUC ratio within the 0.80–1.25 range.

Results



Overall, for all three drugs, the simulated AUC ratio values in children aged 6 to 12 were consistently within the 0.5 to 2-fold range. This suggests that differences in drug exposure for this age group are likely insignificant, regardless of the method used. However, BSA-based dosing tended to slightly higher exposures than BWT-based doses for children with BMI <5th percentile, and slightly lower exposures in children with BMI >95th percentile.

	N total	Azithromycin		Raltegravir		Itraconazole	
		N with AUC ratio (0.8-1.25)	% within the 0.8-1.25 range	N with AUC ratio (0.8-1.25)	% within the 0.8-1.25 range	N with AUC ratio (0.8-1.25)	% within the 0.8-1.25 range
5th percentile	705	478	67.8	652	92.48	406	57.59
Median (5-95 th) children	4171	4154	99.59	4139	99.23	3805	91.23
95th percentile	124	117	94.35	105	84.68	86	69.35

Conclusions

- **Interchangeability:** BWT (Body Weight) and BSA (Body Surface Area) dosing are largely interchangeable for median weight children (age 6-12) with minor discrepancies observed in 5th and 95th percentile subjects but within acceptable AUC ratio range (0.5-2-fold).
- The conclusions from our simulation align closely with those from Hughes et al. (1), which examined growth hormone dosing using both BSA and BWT methods. Hughes et al. identified a slight diminished pharmacodynamic response with BSA-based dosing, although both approaches are generally comparable, with significant differences primarily emerging in cases of extreme weight (2).
- **Correlation and Variability:** strong correlation between AUCs for BWT and BSA dosing shown by high R² values. Clinical rounding of doses introduces variability beyond simulation predictions.
- **Factors Influencing Dosing Choice:** Drug's ADME/PK properties and therapeutic index. Population age can affect the choice of dosing strategy.
- **Further Research:** Extend studies to other age ranges such as neonates or infants to evaluate physiological differences such as maturation (3). Increase the number of drugs studied to validate findings across a wider spectrum.

References

1. Hughes IP, Harris M, Cotterill A, Ambler G, Cowell CT, Cutfield WS, Werther G, Choong CS. Comparison of weight- vs body surface area-based growth hormone dosing for children: implications for response. Clin Endocrinol (Oxf). 2014 Mar;80(3):384-94. doi: 10.1111/cen.12315. Epub 2013 Sep 18. PMID: 23968547.
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3. Reed MD, van den Anker J. Developmental Pharmacotherapy: The Interface Between Ontogeny and Drug Effect. J Clin Pharmacol. 2018 Oct;58 Suppl 10:S7-S9. doi: 10.1002/jcph.1317. PMID: 30248194.