Background and Objectives

First strategy for paediatric dosing of anti-infectives is to target exposures similar to successfully treated adults. Scaling pharmacokinetics (PK) is a key first step.

- **Body size alone** explains most of the changes down to 2-3 years of age.
- Allometric scaling (1) describes the nonlinear effect of body size on PK
- Other factors, including maturation, mostly in children <3 years old (2)

Same mg/kg dose in children and adults causes under-dosing (Figure 1). Even with no info available, allometry is a better guess than constant mg/kg (3)

Paediatric dosing regimens still incorrectly use constant mg/kg dosing as first "best-guess", possibly because of the difficulty due to the non-linearity.

The objective of this work is to bridge this gap by proposing an intuitive and easy-to-use tool to assist researchers not conversant in PK modelling to design and evaluate paediatric dosing regimens.

Methods

The tool was designed using Microsoft Excel,

- chosen for its ease of use and ubiquity
- familiarity amongst clinicians
- with easy steps to follow and
- results displayed in a graphical form in real-time

The tool uses allometric scaling to adjust for the effect of body size on clearance. It targets the same exposure in terms of area under the time-concentration curve (AUC) as adults. It shows the expected median exposure in the smallest and largest child in each weight band.

Features

- analysis of multiple drugs in a fixed-dose combination (FDC)
- use of standard dosing weight-bands or customised weight bands can be explored
- possibility of including the effect of maturation (if known for the drug)

Results – WHO Paediatric Dosing Tool

The user selects

- the target adult dose for each drug
- the reference adults weight (band)
- Table C sets the strength of each component in the FDC
- Table D allows the user to adjust the acceptable exposure ranges
- Optionally, a maturation function can be specified (if known)

- The number of tablets in each weight-band can be set
- New weight-bands can be explored in 1 kg increments
- The expected typical AUC – the lowest and highest values within each band – is shown against the target (adult exposure)

DISCUSSION

The tool is only meant to provide general guidelines, mostly based on the theory of allometric scaling, accounting for the effect of body size on PK

Allometric scaling alone works well down to 2 years of age, but below that, immature organ function may cause clearance to be lower than body size alone would predict. This is explored in the tool but is strongly drug-specific

Other factors – not accounted for in the tool - may have a large impact, e.g.: lower protein binding in young children, differences in drug formulation, or poor absorption.

Additionally, terminal half life is generally shorter in children, so targeting the same AUC – as in this tool - may achieve higher C\text{\textsubscript{\text{max}}} and lower C\text{\textsubscript{\text{avg}}}.

To avoid toxicity (high C\text{\textsubscript{\text{max}}}) or poor efficacy (low C\text{\textsubscript{\text{avg}}}) it may be necessary to switch from QD to BID dosing in smaller children.

Only typical values are shown and no between subject variability is included here. Some drugs may be characterised by large variability

Limitations

The purpose of the tool is to assist in the design of clinical trials for dosing in paediatrics, and is meant as a first step, not a substitute to confirmatory studies.

The use of this tool (and thus allometric scaling) for study design would represent a significant step away from the constant mg/kg paradigm, possibly leading to improvements in the efficacy of paediatric dosing trials.

References


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An easy-to-use Paediatric Dosing Tool – Because one mg/kg dose does NOT fit all.

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