Clinical Pharmacokinetics

Online supplementary material

Evidence based design of fixed-dose combinations – principles and application to pediatric anti-tuberculosis treatment

Elin M Svensson¹, Gunnar Yngman¹, Paolo Denti³, Helen McIlleron³, Maria C Kjellsson¹, Mats O Karlsson¹

1. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
2. Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands
3. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Corresponding author
Elin M Svensson, elin.svensson@farmbio.uu.se

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Breakpoint estimation

Estimation of a break-point (BP), which is intrinsically of discontinuous nature, can be difficult and sensitive to initial estimates, especially with gradient-based estimation methods. Three different continuous functions (Equation 1-3) mimicking the discontinuous step \{0 if individualization variable (IV) < BP, 1 if IV > BP\} were evaluated to mitigate this difficulty. The constant $\gamma$ in the following equations determines the steepness of the approximate step-function.

\[
STEP_{power} = \frac{IV^\gamma}{IV^\gamma + BP^\gamma}
\]  \hspace{1cm} (1)

\[
STEP_{exponential} = \frac{e^{\gamma \cdot IV}}{e^{\gamma \cdot IV} + e^{\gamma \cdot BP}}
\]  \hspace{1cm} (2)

\[
STEP_{logistic} = \frac{1}{1 + e^{-\gamma \cdot (IV-BP)}}
\]  \hspace{1cm} (3)

The power function (Equation 1) has the drawback that the steepness of the function is depending on the value of the BP making it difficult to select $\gamma$. The function of exponentials (Equation 2) necessitates calculation of very large exponential when IV, BP, and/or $\gamma$ become large and this may cause numerical problems. The logistic function (Equation 3) has neither of these two drawbacks and has therefore been selected.

Simulations and estimations were performed to evaluate the stability of the BP estimation procedure. Both gradient-based and sampling-based estimation methods implemented in NONMEM 7.3 were considered. The expectation-maximization sampling-based methods require random variability in the parameters for efficient estimation. Since the BP value that should be estimated must be one fixed value without random variability, use of these methods was excluded. The first-order (FO) gradient based method was found to be sensitive to initial estimated at higher values of $\gamma$. To overcome this, a sequential estimation process was implemented where one starts from a low $\gamma$ value, estimate all parameters, then increases the $\gamma$ value and estimate again with the initial values for the parameters set to the final result from the previous estimation. This procedure using the $\gamma$ values 0.5, 5, 50 and 500 was found to be stable and $\gamma=500$ results in a close approximation of a discontinuous step.
Age-weight distribution for pediatric population with TB

An accurate distribution of population characteristics is a prerequisite for a relevant optimization procedure. To generate a large and representative distribution of body weights of children of both genders with pulmonary TB an adjusted growth reference was constructed. The basis was the WHO international growth reference for children between 0 and 10 years [1], and for older children (not covered by the WHO references) the American NHANES CDC growth standards [2]. The percentile curves in these references can be described by the LMS-formula based on values for the median weight (M), the coefficient of variance (L) and the skewness (S) per age in months (i) and gender (g) [3]. According to this formula, body weights can be simulated using Equation 4 where $Z \sim N(0,1)$.

$$Weight_{g,i} = M_{g,i} \cdot (Z \cdot L_{g,i} \cdot S_{g,i})^{1/L_{g,i}} \quad (4)$$

The concern with using the standard references was that children with TB are known to be lighter than healthy children of the same age, hence the standard reference would generate an unrepresentative population. To correct for this, age-weight data from four pediatric studies were used to derive a function to adjust the median value to better represent children with pulmonary TB. Combined, the studies included 642 children between 5 months and 13 years of age from South Africa, India, and Malawi. A large age-weight dataset with uniform age distribution between 0 and 13 years was simulated using the standard references, and the median weight per age range were calculated for both the real and the simulated data. A correction factor for each age range was calculated by dividing the real median weight with the simulated median weight (Table S1). A nonlinear function to describe continuously the relationship between the correction factor and age in months was selected by visual fitting and is shown in Figure S2. The selected function is given by Equation 5 and the adjusted weight calculation by Equation 6.

$$correction\_factor_i = 0.95 - \frac{0.3}{1 + e^{-0.4(age-50)}} \quad (5)$$

$$Weight_{g,i} = M_{g,i} \cdot correction\_factor_i \cdot (Z \cdot L_{g,i} \cdot S_{g,i})^{1/L_{g,i}} \quad (6)$$
Table S1. Age-weight data used to derive the correction factor per age range adjusting the median standard growth references for the lower weight in children with TB. Correction factor = median observed weight in children with TB/median weight simulated from standard growth references.

| Age range (years) | Simulated Median age (years) | Simulated Median weight (kg) | Observed Median age (years) | Observed Median weight (kg) | Correction factor |
|-------------------|------------------------------|------------------------------|-----------------------------|------------------------------|-------------------|
| 0-1               | 0.5                          | 7.23                         | 131                         | 0.58                         | 6.70              | 0.93              |
| 1-2               | 1.5                          | 10.4                         | 111                         | 1.42                         | 9.60              | 0.93              |
| 2-3               | 2.5                          | 12.9                         | 73                          | 2.33                         | 11.2              | 0.87              |
| 3-4               | 3.5                          | 15.0                         | 52                          | 3.51                         | 13.3              | 0.88              |
| 4-6               | 5.0                          | 18.2                         | 70                          | 4.60                         | 14.8              | 0.81              |
| 6-9               | 7.5                          | 23.7                         | 96                          | 7.07                         | 18.0              | 0.76              |
| 9-12              | 10.5                         | 33.5                         | 66                          | 10.0                         | 23.1              | 0.69              |
| 12-13             | 12.5                         | 43.2                         | 43                          | 12.3                         | 28.3              | 0.66              |

Figure S2. The continuous function for the relationship between age and the correction factor adjusting the median of the standard growth references for the lower weight in children with TB. The black dots are the correction factors calculated in defined age-ranges (Table S1) and the line shows the continuous function (Equation 5).
The agreement between the observed age-weight data and the distributions simulated with the standard and the adjusted growth reference were evaluated visually (Figure S3). The distribution simulated from the standard growth reference clearly over-predicts weight-for-age, while the distribution simulated using the correction factor agrees well with the observed data.

Figure S3. Evaluation of agreement between the observed age-weight distribution and distributions simulated from the standard and adjusted growth reference charts. Grey rings represent simulated data, red dots observed data and the lines are smoothed averages of the simulated (black) and observed (dark red) data.
Generic example code 3-drug FDC

;; Description: FDC optimization, 3 drugs, 3 break-points
;; Author: Elin Svensson, elin.svensson@farmbio.uu.se
;; Please feel welcome to contact me with any questions or if you need help with the implementation.

$SIZES MAXIDS=150000 NO=500
$PROBLEM 3 BP, Logistic (500) BP model
$INPUT ID BW CL DRUG DV
$DATA data.csv IGNORE=@
; ID – subject identification number
; BW – Individualization variable, here body weight
; CL – Individual apparent CL for each drug, used to calculate steady state exposure
; DRUG – Flag to indicate to differentiate included drugs, here 1,2 and 3
; DV – Dependent variable to include in utility function, here set to zero (strive to minimize deviation
; between target and individual exposure)

$PRED
;--- Slope factor for BP model
GAM = X ; X should be iteratively increased in a sequential optimization, e.g. 0.5, 5, 50 and 500

;--- Define doses and target AUCs for each drug

DOSE1 = THETA(1)
DINC = DOSE1
TARGET = AAA
ER = ETA(1)

IF(DRUG.EQ.2) THEN
    DOSE1 = THETA(2)
    DINC = DOSE1
    TARGET = BBB
    ER = ETA(2)
ENDIF

IF(DRUG.EQ.3) THEN
    DOSE1 = THETA(3)
    DINC = DOSE1
    TARGET = CCC
    ER = ETA(3)
ENDIF
;--- Break points

BP1 = THETA(4)
BP2 = BP1 + THETA(5)
BP3 = BP2 + THETA(6)

DOSE2 = DINC * (1 / (1 + EXP(-2 * GAM * (BW - BP1))))
DOSE3 = DINC * (1 / (1 + EXP(-2 * GAM * (BW - BP2))))
DOSE4 = DINC * (1 / (1 + EXP(-2 * GAM * (BW - BP3))))

DOSEFINAL = DOSE1 + DOSE2 + DOSE3 + DOSE4

;--- AUCs

AUC = DOSEFINAL/CL

;--- Optimize dose

Y = LOG(AUC) - LOG(TARGET) + ER
DIFF = LOG(AUC) - LOG(TARGET)

$THETA
(0, X1) ; DOSE DRUG 1
(0, X2) ; DOSE DRUG 2
(0, X3) ; DOSE DRUG 3
(LOWLIM, X4) ; BP 1
(0, X5) ; BP 2
(0, X6) ; BP 3

$OMEGA
0.01 FIX
0.01 FIX
0.01 FIX

$ESTIMATION METHOD=0 MAX=9999 PRINT=1
References
1. World Health Organization. WHO child growth standards length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. (Department of Nutrition for Health and Development, 2006). at <http://www.who.int/childgrowth/standards/Technical_report.pdf>.

2. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat. 11. 2002;1–190.

3. Cole T, Green P. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat. Med. 1992;11:1305–19.