



Objective

To develop a model based methodology to guide design of FDCs and selection of an exposure based dosing regimen with the application to anti-tuberculosis (TB) drugs for children.

Methods

A rational approach for selection of optimal covariate-based dosing for single drugs has previously been developed (Fig. 1) [1]. Here, this methodology was expanded to accommodate several drugs simultaneously and to estimate tablet content for multiple components. Further, the relationship between estimation stability and choice of equation mimicking the discontinuous step between dose-levels was investigated.

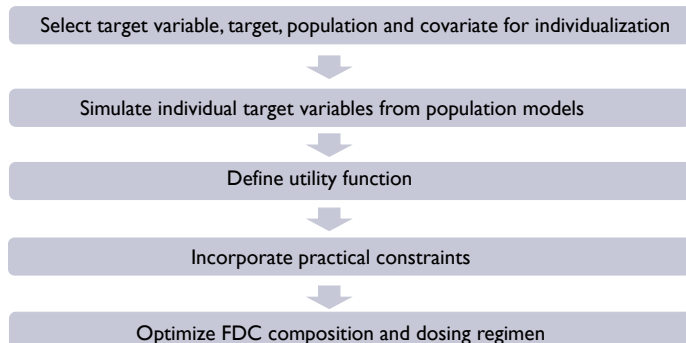


Fig. 1: Flow chart outlining the approach for selection of optimal covariate-based dosing.

For the example of pediatric anti-TB FDCs

- Target variable: AUCs of the four standard anti-TB drugs
- Targets: calculated from current adult dosing recommendations
- Population: children with a uniform age distribution between 2-10 years
- Covariate for individualization: body weight

Weights were simulated based on the WHO child growth standards [2] assuming log-normal distribution and truncated at 30 kg. Individual clearances for rifampicin, isoniazid, pyrazinamide and ethambutol were simulated using published population PK models [3-6] and allometric scaling.

Estimation of optimal drug content per tablet and break points for change of dose were based on minimizing the deviation between the logarithm of individual AUC and target AUC (the utility function, Eq. 1), hence weighting too low exposure as more serious compared to too high exposures.

$$Y = \ln(AUC_{target}) - \ln(AUC_{individual}) + \varepsilon \quad \text{Eq. 1}$$

dependent variable = 0, SIGMA fixed to small value

The equations used to mimic the step between dose levels were an sigmoid Emax function (Eq. 2) and a nonlinear function of exponentials (Eq. 3). The equations were evaluated on datasets with different ranges of body weight and number of individuals. The difference between dose levels was fixed to one tablet and estimation carried out using FOCE in NONMEM 7.2.

$$\text{Step1} = \frac{BW^{GAM}}{BW^{GAM} + BP^{GAM}} \quad \text{Eq. 2}$$

$$\text{Step2} = \frac{e^{BW \times GAM}}{e^{BW \times GAM} + e^{BP \times GAM}} \quad \text{Eq. 3}$$

BW=body weight, BP=break point, GAM=sigmoidicity factor

Results

Equation 3 was successfully used to mimic the step between dose-levels and found preferable over equation 2 since the steepness is independent of the value of the break point. However, estimation was found unstable and dependent on initial estimates for high sigmoidicity factors. This could be overcome by sequential estimation of models with increasing steepness of the step function and successive update of initial estimates. Stable estimates of optimal tablet content and break points for dose increase were obtained (Tab. 1).

Tab. 1: Estimates of doses and break points for pediatric anti-TB FDC tables and relative RMSE when allowing 1-4 dose levels.

Parameter	1 dose level	2 dose levels	3 dose levels	4 dose levels
Tablet content RIF (mg)	217	119	86.1	67.3
Tablet content PYR (mg)	580	317	230	180
Tablet content INH (mg)	60.3	32.9	23.9	18.7
Tablet content ETH (mg)	400	219	159	124
Break point 1 (kg)		13.6	9.62	6.68
Break point 2 (kg)			18.2	13.2
Break point 3 (kg)				20.9
Relative RMSE RIF (%)	74.7	72.8	69.1	68.6
Relative RMSE PYR (%)	29.7	27.6	23.0	22.0
Relative RMSE INH (%)	72.5	71.0	67.6	66.6
Relative RMSE ETH (%)	60.3	59.4	55.2	54.7

The benefit of increasing number of dose levels depends on the covariate relationship and the inter-individual variability (IIV) in the drug's PK. For example, relative RMSE of the exposure decreased more with increasing number of levels for pyrazinamide (low IIV) compared to rifampicin (high IIV).

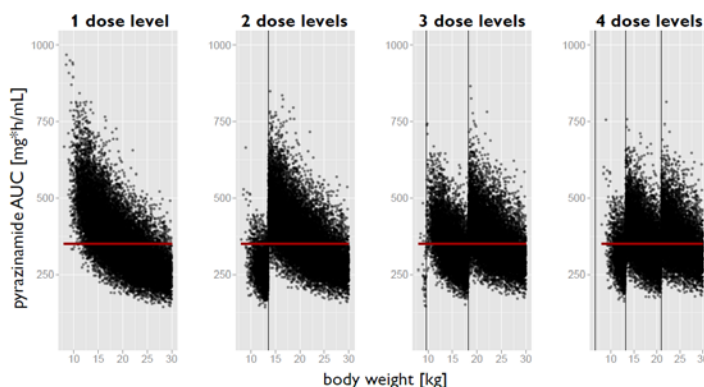


Fig. 2: Pyrazinamide exposure for different body weights when allowing 1-4 dose levels. Red line = target exposure, black lines = break point for dose change.

Conclusions

A flexible methodology for design of FDCs was successfully developed. Anti-TB drugs were used as an example, but current results should not be interpreted as recommendations for FDC development. For such a proposal, the methodology should be applied with pediatric population PK models, clinically valid targets and practical constraints such as co-formulation aspects.

References

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