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Combined proportional and additive residual error models in population pharmacokinetic modelling

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ABSTRACT

Introduction: In pharmacokinetic modelling, a combined proportional and additive residual error model is often preferred over a proportional or additive residual error model. Different approaches have been proposed, but a comparison between approaches is still lacking.
Methods: The theoretical background of the methods is described. Method VAR assumes that the variance of the residual error is the sum of the statistically independent proportional and additive components; this method can be coded in three ways. Method SD assumes that the standard deviation of the residual error is the sum of the proportional and additive components. Using datasets from literature and simulations based on these datasets, the methods are compared using NONMEM.
Results: The different coding of methods VAR yield identical results. Using method SD, the values of the parameters describing residual error are lower than for method VAR, but the values of the structural parameters and their inter-individual variability are hardly affected by the choice of the method.
Conclusion: Both methods are valid approaches in combined proportional and additive residual error modelling, and selection may be based on OFV. When the result of an analysis is used for simulation purposes, it is essential that the simulation tool uses the same method as used during analysis.

1. Introduction

Selecting the appropriate residual error (also denoted residual unexplained variability) model is an important step in population pharmacokinetic and pharmacodynamic modelling (Dosne et al., 2016). In pharmacokinetic modelling, a combined proportional and additive residual error model is often found to describe the data better than a proportional or additive error model, as can be concluded from many publications. Moreover, this model is logical from a theoretical point of view, with a proportional component related to the proportional relationship between concentration and instrumental response in bioanalysis, as well as an additive component, among others related to instrumental noise level, resulting in a lower limit of quantification. For other sources of residual error, e.g. model misspecification, the relationship between concentration and residual error is less obvious. A general framework for residual error modelling incorporating scedasticity of variance and distribution shape was published recently (Dosne et al., 2016).

Little attention has been paid in literature to the fact that the combined residual error model can be modelled in different ways. The existence of different approaches has been discussed in discussion groups (NONMEM Users Network, 2001; PharmPK Discussion, 2013), but a comparison between these approaches is still lacking.

It is the aim of this paper to show the background of methods for combined proportional and additive residual error modelling, to compare the results obtained with different methods, and to discuss the impact of the methods.

2. Methods

2.1. Residual Error Models

The combined proportional and additive residual error model can be implemented in different ways, dependent on the assumption about the mathematical relationship describing the variance or standard deviation of the residual error:

- Method VAR assumes two independent sources of error, a proportional and an additive component, and the variance of the residual error is the sum of both components.

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- Method SD assumes one source of residual error, and the standard deviation of the residual error is the sum of a proportional and an additive component.

Both methods are described in detail below. NONMEM (Icon Development Solutions, Hanover, MD, USA) symbols and coding were used throughout this paper.

2.1.1. Method VAR.1

The combined proportional and additive residual error model is described in the NONMEM manual (Boeckmann et al., 2013) by the following code in the $ERROR block:

$$Y = F + F*EPS(1) + EPS(2) \quad (1)$$

where Y is the modelled value for the observed variable under the statistical model, F is the model predicted value, and EPS(1) and EPS(2) are random values from normal distributions N(0,SIGMA(1)) and N (0,SIGMA(2)), respectively.

Eq. (1) implies that the proportional and additive components are assumed to be statistically independent. The residual error, i.e., the difference between Y and F is explained by the sum of both independent components F*EPS(1) and EPS(2).

The standard deviation of the residual error, W, is obtained from the square root of the variance, which in turn is the sum of the variances of both components, resulting in:

$$W = SQRT(SIGMA(1)*F*F + SIGMA(2)) \quad (2)$$

and can be used to convert the residual to the weighted residual (IWRES) by dividing the residual by W (see below, Eq. (11)).

2.1.2. Method VAR.2

The following code may be used instead of Eq. (1):

$$Y = F + SD1*F*EPS(1) + SD2*EPS(2) \quad (3)$$

where SD1 and SD2 are model parameters (THETAs) that can be estimated by fixing the variances of EPS(1) and EPS(2) to 1 by

$$\$SIGMA\ 1\ FIX\ 1\ FIX \quad (4)$$

Using Eq. (3), the standard deviation W can be obtained from:

$$W = SQRT((SD1*F)** 2+ SD2**2) \quad (5)$$

Although Eqs. (1) and (3) produce identical results (see Results section), the output provided by NONMEM is different. Eq. (1) provides estimates of SIGMA(1) and SIGMA(2), which can be converted to standard deviations SD1 and SD2 by:

$$SDn = (SIGMAn)^{0.5} \quad (6)$$

The corresponding standard errors can be obtained from the law of error propagation:

$$SE^2(SDn) = \left(, \frac{\partial SDn}{\partial SIGMAn}\right)^2 \cdot SE^2(SIGMAn) \quad (7)$$

where the partial derivative is obtained from Eq. (6), resulting in $1/(2 \cdot SD_n)$, so Eq. (7) can be simplified to:

$$SE(SDn) = \left(\frac{1}{2 \cdot SDn}\right) \cdot SE(SIGMAn) \quad (8)$$

Eq. (3) provides THETA values for SD1 and SD2, with the corresponding standard errors. After rearrangement of Eqs. (6)–(8), the standard errors for the corresponding variances may be calculated.

2.1.3. Method VAR.3

Alternatively, since the standard deviation is given by Eq. (5), the model may be coded as:

$$Y = F + W*EPS(1) \quad (9)$$

Note that method VAR.3 (Eq. (9)) uses a single EPS (with $SIGMA 1 FIX), whereas methods VAR.1 (Eq. (1)) and VAR.2 (Eq. (3)) use two EPS values.

2.1.4. Method SD

Method SD assumes that the standard deviation of the residual error is the sum of the proportional and additive component. Therefore the standard deviation is modelled as a function of F according to:

$$W = SD1*F + SD2 \quad (10)$$

Using Eqs. (9) and (10), the error model may be coded with a single EPS (with $SIGMA 1 FIX).

2.2. Examples

2.2.1. Example 1

The datafile was obtained from the website of the American College of Clinical Pharmacology (no longer provided by this website), and can be found now at Certara Forum (2016). There were 100 subjects, given a dose of 100 or 250 mg, and each individual was sampled at 15 time points post-dose.

The pharmacokinetic model was a one-compartment model with clearance (*CL*) and volume of distribution (*V*) using subroutines ADVAN1 and TRANS2, with inter-individual variability in both parameters, assuming a log-normal distribution. Covariates were not used in the present analysis.

2.2.2. Example 2

The datafile was a modified version of the datafile of example 1, where the doses of 100 mg, as given to the first 50 patients, were changed to 150 mg, with a corresponding conversion of the observed concentrations (DV) by multiplying by 1.5, assuming linear pharmacokinetics.

2.3. Simulations

Simulated datasets were generated using each of the methods VAR.1, VAR.2, VAR.3 and SD, and analyzed using the same method as used for generation and using each of the other methods. For each example and each combination of methods, 1000 datasets were generated and analyzed. To allow a comparison of the methods for analysis with identical datasets, the seed for the random generator was the same in all simulations.

2.4. Calculations

The root mean squared error (RMSE) of the individual weighted residuals (IWRES) was calculated, where IWRES was obtained from:

$$IWRES = (DV–F)/W \quad (11)$$

All calculations were performed using NONMEM version 7.3.0 (Icon Development Solutions, Hanover, MD, USA. http://www.iconplc.com/innovation/nonmem/) using the first-order conditional estimation (FOCE) method with interaction. Nonparametric 95% confidence intervals were obtained by bootstrap analysis using PLT Tools version 5.5.0 (PLTsoft, San Francisco, CA. http://www.PLTsoft.com/) and R version 3.3.1 (R Foundation for Statistical Computing. https://www.R-project.org).

The methods and equations for combined proportional and additive residual error modelling are summarized in Table 1.

3. Results

3.1. Example 1

The results are summarized in Table 2. Methods VAR.1, VAR.2 and VAR.3 yielded identical results, when for method VAR.1 the values of