Assessment of optimal sampling times for estimation of AUC in Therapeutic Drug Monitoring by Monte Carlo simulations

Implemented in MW\Pharm version 3.60 (date 30-6-2004)

Aim

The aim of the procedure is to determine the optimal sampling times for the assessment of AUC after administration of a drug, either as a single dose or during a regular dosing schedule. For a single dose, AUC is defined as the total area under the plasma concentration time profile from time zero to infinity; for a regular dosing interval at steady state, AUC is defined as the area under the plasma concentration time profile over one dosing interval of duration τ. Assuming linear pharmacokinetics, AUC equals Dose/CL for an intravenous administration, and Dose.F/CL for an extravascular administration.

Instructions

The first step is the selection of a patient to be used as a template for the medication history, or a new patient history can be entered and saved. The dosing schedule can be chosen freely, and does not need to be a regular dosing schedule. Logically the dosing schedule is similar to that used in the treatment of patients for which the plasma concentration is monitored, but this is not a necessary restriction.
A time schedule for concentration measurement is optional (see below).

To allow the determination of optimal sampling times by Monte Carlo simulation, the following must be known:

a) Pharmacokinetic model, including route of administration.
b) Pharmacokinetic population parameters and their interindividual standard deviation; if applicable, also the covariance between parameters must be known (usually covariance is assumed to be absent). In addition the distribution of individual parameters must be known. Usually a lognormal distribution is preferred to avoid extremely small parameter values.
c) Residual error model. Usually it is assumed that the residual error is a function of the plasma concentration. The use of a polynomial to describe this relationship is a very flexible approach. To take into account other sources of error, e.g. model misspecification, the actual residual error can be increased by defining a factor GammaSD larger than 1, e.g. 2 (in the Fitting screen; see manual to MW\Pharm version 3.60).

Monte Carlo data generation

The Monte Carlo optimal sampling procedure can be started from the main menu, after selection of a patient as a template:

- <5> Medication history
- <F10> Graphical presentation

- <F10> Fitting screen
- <F5> Monte Carlo optimal sampling procedure

1. Time of start sampling interval

The default time of start of the sampling interval is the time point of the last dose in the medication history, but can be chosen freely.

2. Sampling interval

The duration of the sampling interval is by default the dosing interval of the last dose, but can be chosen freely.

3. Sampling time schedule

The sampling time schedule, i.e. the time points from which the optimal time points are selected during the data analysis, can be chosen in two ways:

a. Time points with fixed time intervals
The time resolution can be chosen freely; default is 1 hour, minimum is determined by the available memory.

b. Time schedule of measurements in the medication history

4. Number of data sets

The number of data sets to be generated. The default value is 1000 for a fast analysis. For more accurate results, the maximum number of 10,000 sets is recommended.

5. Save data sets

The generated data sets can be saved for (re-)analysis at a later time.

6. Load data sets

Saved data sets can be reloaded for (re-)analysis. Please note that the selection of all options until this points must be exactly equal to that during data generation; if not, the results may be invalid. This cannot be checked by the program, and must be done by the user.

7. Start data generation

For each individual the pharmacokinetic parameters are randomly drawn from a population as defined by mean, standard deviation (SD), covariance and distribution pattern. Then the ‘true’ plasma concentration values at predefined time points are calculated using the individual pharmacokinetic parameters, and the ‘measured’ plasma concentrations are randomly drawn around the ‘true’ values, assuming a specified level of assay error, and taking into account the specified factor GammaSD.

Data analysis

1. Parameter to be optimized

In current version, only AUC can be chosen as the parameter to be optimized. See under Aim for the definition of AUC.

2. Methods for parameter estimation

a. Bayesian analysis
For each simulated patient the individual pharmacokinetic parameters are estimated by a Bayesian fitting procedure, using the population data set as prior distribution. The measurement are weighted according to their assay error pattern. The AUC is calculated as Dose/CL in case of intravenous administration, and as Dose.F/CL in case of extravascular administration.
Note: Determination of an optimal sampling schedule by Bayesian parameter estimation from real patient data was applied by Cremers et al (Nephrol Dial Transplant. 2003;18:1201-1208).

b. Regression-analysis
The AUC of the individual patients is obtained in two steps. First, the relationship between the true AUC and the measured concentrations is obtained by multiple linear regression of the data of all patients:

AUC = P0 + P1 * C1 + P2 * C2 + ...

where P1 is the coefficient of C1, the concentration at time point 1, et cetera. The coefficient P0 is the intercept that can be estimated by linear regression or kept fixed to zero (to be selected at option 3). The true AUC of each patient is obtained from the individual pharmacokinetic parameters (Dose/CL in case of intravenous administration, and as Dose.F/CL in case of extravascular administration).
Then the AUC of each individual is estimated from the equation, using the same values for the coefficients for each patient.
Note: Determination of an optimal sampling schedule by regression analysis from real patient data is nowadays the standard approach, although the method has been criticised.

c. Trapezoidal rule
The AUC of the individual patients is estimated in two steps. First, the AUC of each simulated patient is calculated by the trapezoidal rule, using the measured concentrations. The concentration at the start and end of the AUC interval were assumed to be zero, unless the concentration at these time points was measured. This procedure allows an estimation of the AUC even in the case of one measurement. Second, the AUC is determined in the same way, using the exact plasma concentrations calculated from the population parameters (AUC_{pop}). Also, the exact AUC (AUC_{exact}) is calculated from the population pharmacokinetic parameters (Dose/CL in case of intravenous administration, and as Dose.F/CL in case of extravascular administration). Finally, the AUC of each individual is obtained by

multiplying the estimated AUC with the ratio of AUC_{exact} and AUC_{pop} ($F_{AUC} = AUC_{exact} / AUC_{pop}$).
The method can be modified by application of a 'bias correction' (to be selected at option 3). In this case the correction factor is adusted in such a way that the bias is exactly zero. Consequently, the AUC is recalculated. Usually this bias correction affects the RMSE only slightly, either downwards or upwards.

Note: The Trapezoidal rule approach (and the Sum of concentrations approach; see under d) cannot be applied in case of real patient data, unless plausible population parameters are known to allow the calculation of F_{AUC} with satisfactory precision.

d. Sum of concentrations
This method is almost similar to the trapezoidal rule method. Instead of calculating AUC, the sum of measured concentrations is used as a first estimate of AUC. Conversion of units of concentration to AUC is done automatically in the correction factor F_{sum}, which includes here the factor with respect to time.

3. (option dependent on previous choice; see above).

4. Number of samples

The number of samples for each patient can be selected. The default value is 4, the minimum is 1, and the maximum is the number of samples in the generated data set. The optimal sampling procedure is applied also for any smaller number of samples (e.g. if the number is 4, the procedure is applied for 1, 2, 3, and 4 samples). Of course, the higher the number of measurements, the better the accuracy and precision of the estimated AUC.

5. Number of results shown

The number of results to be shown on the screen can be selected. Default is 4, i.e. the four time schedules with the lowest RMSE are shown on the screen.

6. Search algorithm

To find the optimal time schedule, two algorithms are implemented:
a. *Systematic search*: All possible combinations of the available time points are tested. This procedure warrants that the optimal sampling schedule is found. However, the number of combinations, and consequently, the computing time, increases exponentially with the number of sampling times.
b. *Sequential*: This algorithm reduces the number of combinations by selecting time schedules with N samples based on the optimal sampling times with N-1 samples. For one sampling point, the systematic procedure is applied. For two sampling points the best M sampling points are combined with any other available sampling time. The number M can be chosen arbitrarily; the higher the number M, the most robust and time consuming the procedure will be.

7. Start analysis

During the calculations, the evaluated time schedules are shown on the screen, in order of increasing RMSE.

Evaluation

For each time schedule, the accuracy and precision of the calculated AUC are evaluated by comparing their mean error (ME) and root mean squared error (RMSE), respectively. In addition, the correlation coefficient (r) of the relationship between the true AUC and the estimated AUC for each patient is calculated. Both RMSE and ME are expressed as fraction of the exact AUC as obtained from the population parameters (AUC_{exact}).
RMSE is applied as the criterion for the optimal sampling schedule, since it reflects the degree of imprecision of an estimated AUC for an individual patient. Therefore the evaluated time schedule are shown in a ranking order determined by the minimum RMSE.

Discussion

The application of Monte Carlo simulations for the development of an optimal sampling schedule has several important advantages over the traditional approach using a patient study:

- if a plausible set of pharmacokinetic population parameters is available, a patient study is not needed, thus resulting in a decrease of time, costs, and discomfort for patients;
- the results are more precise, since a large number of patients can be chosen, reducing the variability of the results;
- if a sufficiently large number of patients is chosen, a validation study group is not necessary thus resulting in a decrease of time, costs, and discomfort for patient;
- the results are more accurate, since approximations in the calculation of AUC are avoided.

Of course this method has some restrictions. Obviously the correct optimal sampling schedule is obtained only if the set of pharmacokinetic population parameters is correct. In addition, a disadvantage of any Monte Carlo is that the results are reproducible only if a very large number of samples are analysed, thus increasing the computation time.