COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 127 (2016) 83–93

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

A diagnostic tool for population models using non-compartmental analysis: The *ncappc* package for R

Chayan Acharya[a,*], *Andrew C. Hooker*[a], *Gülbeyaz Yıldız Türkyılmaz*[a,b], *Siv Jönsson*[a], *Mats O. Karlsson*[a]

[a] *Department of Pharmaceutical Biosciences, Uppsala University, P.O. Box 591, SE-751 24 Uppsala, Sweden*
[b] *Ege University, Faculty of Pharmacy, Department of Biopharmaceutics and Pharmacokinetics, 35100 İzmir, Turkey*

ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form
7 December 2015
Accepted 7 January 2016

Keywords:
Non-compartmental analysis (NCA)
PK
NONMEM
Posterior predictive check
Simulation-based diagnostic

ABSTRACT

Background and objective: Non-compartmental analysis (NCA) calculates pharmacokinetic (PK) metrics related to the systemic exposure to a drug following administration, e.g. area under the concentration–time curve and peak concentration. We developed a new package in R, called *ncappc*, to perform (i) a NCA and (ii) simulation-based posterior predictive checks (*ppc*) for a population PK (PopPK) model using NCA metrics.

Methods: The *nca* feature of *ncappc* package estimates the NCA metrics by NCA. The *ppc* feature of *ncappc* estimates the NCA metrics from multiple sets of simulated concentration–time data and compares them with those estimated from the observed data. The diagnostic analysis is performed at the population as well as the individual level. The distribution of the simulated population means of each NCA metric is compared with the corresponding observed population mean. The individual level comparison is performed based on the deviation of the mean of any NCA metric based on simulations for an individual from the corresponding NCA metric obtained from the observed data. The *ncappc* package also reports the normalized prediction distribution error (NPDE) of the simulated NCA metrics for each individual and their distribution within a population.

Results: The *ncappc* produces two default outputs depending on the type of analysis performed, i.e., NCA and PopPK diagnosis. The PopPK diagnosis feature of *ncappc* produces 8 sets of graphical outputs to assess the ability of a population model to simulate the concentration–time profile of a drug and thereby evaluate model adequacy. In addition, tabular outputs are generated showing the values of the NCA metrics estimated from the observed and the simulated data, along with the deviation, NPDE, regression parameters used to estimate the elimination rate constant and the related population statistics.

Conclusions: The *ncappc* package is a versatile and flexible tool-set written in R that successfully estimates NCA metrics from concentration–time data and produces a comprehensive set of graphical and tabular output to summarize the diagnostic results including the model specific outliers. The output is easy to interpret and to use in evaluation of a population PK model. ncappc is freely available on CRAN (http://cran.r-project.org/web/packages/ncappc/index.html/) and GitHub (https://github.com/cacha0227/ncappc/).

* *Corresponding author*. Tel.: +46 18 471 4304.
E-mail address: chayan.acharya@farmbio.uu.se (C. Acharya).

http://dx.doi.org/10.1016/j.cmpb.2016.01.013

1. Introduction

The principal objective of the pharmacokinetics (PK) studies is to understand the kinetics of a drug molecule in terms of absorption, distribution, metabolism and elimination (ADME). PK data analysis can primarily be classified into non-compartmental analysis (NCA) and model-based analysis, where the latter can range from compartment models to physiology-based models [1]. The NCA benefits from fewer assumptions, compared to model-based approaches. In NCA, the area under the curve (AUC), peak observed drug concentration (C_{max}), time of peak concentration (T_{max}), terminal elimination rate constant (Lambda_z), terminal half-life (HL_Lambda_z) and other metrics are estimated to determine the systemic exposure of a drug following administration. NCA is typically an essential part of PK analysis in the field of drug discovery and in richly sampled clinical PK studies. Regulatory decisions regarding bioequivalence studies are often based on comparisons of AUC and C_{max}, in particular. Additionally, NCA may also be used as a diagnostic tool to evaluate the performance of any compartmental population pharmacokinetic (PopPK) models by comparing the NCA metrics obtained from simulated concentration–time data to the same metrics obtained from the observed concentration–time profile. This can provide information on the models ability to provide adequate description of exposure measures that are typically judged as important for richly sampled concentration–time profiles.

A number of software tools (such as Kinetica [2], WinNonlin [3], PK module in R [4], Scientist [5], PKSolver [6]) are available that can perform NCA. As a novelty, we have extended the use of NCA as a pharmacometric model diagnostic tool employing the principles of a posterior predictive check [7] with the NCA metrics as test statistics. In this article we report a simulation-based diagnostic package, called *ncappc*, written in R [8] that (i) provides a simple and flexible method to estimate the NCA metrics from the observed data and (ii) compares them with the same metric estimated from multiple data sets simulated using the PopPK model to be diagnosed. Thus *ncappc* helps to bridge the gap between NCA and population model analyses. *ncappc* package can potentially facilitate the early stage of the drug discovery process by evaluating the performance of the related PopPK model and identify the model specific outliers.

2. Methods

2.1. Implementation and the usage of the ncappc package

The *ncappc* package is implemented in R and accepts a set of input arguments, resulting in certain processing of data and output production. Table 1 depicts the list of acceptable arguments with default values of the arguments. The names of most of the NCA metrics estimated by the *ncappc* function are consistent with those used in WinNonlin [3]. A comparison of NCA metrics obtained by the *ncappc* package and WinNonlin showed no discrepancies and the results can be found in the Supplementary material-I.

obsFile and *simFile* arguments, used in *ncappc*, represent the observed and the simulated data. The default values of these two arguments are "nca_original.npctab.dta" and "nca_simulation.1.npctab.dta", respectively. To perform NCA, *obsFile* argument should be adjusted to the correct name of the observed data file. If *simFile* argument is NULL and the working directory does not contain "nca_simulation.1.npctab.dta", only *nca* feature of this package will be executed. The name of the simulation output file, structured as is common in table files of many software including NONMEM [9] is supplied via *simFile* argument to use the *ppc* feature of the package. All other arguments are optional and their default value may be adjusted according to the description given in Table 1.

There are three arguments (namely *str1Nm*, *str2Nm* and *str3Nm*) in *ncappc* that can be used to stratify the study population. For a single layer of stratification any of these arguments can be used. If they are used in combination, the population is stratified into nested layers, where *str1Nm*, *str2Nm* and *str3Nm* represent the 1st, 2nd and 3rd levels of stratification, respectively.

If no units are supplied for the dose, time or concentration, *ncappc* labels the NCA metrics with appropriate dimensionality in terms of mass (*M*), length (*L*) and time (*T*). Fig. 1 displays the workflow of this function. If the *simFile* argument is omitted only NCA on observed data is performed while inclusion of the *simFile* argument results in both NCA calculations and the *ppc*-based diagnostics. Details of the output generated by *ncappc* package are described in the Supplementary material-II. In brief, the NCA feature produces two sets of figures displaying the concentration vs. time profile for each individual within a certain population group and the histogram of four NCA metrics (AUClast, AUCINF_obs, C_{max} and T_{max}) estimated from the observed data (see the Supplementary material-I for the definitions). Additionally, two tables are produced representing the estimated individual values of the NCA metrics obtained from the observed data and the values of various population statistics of each of the NCA metrics estimated from the observed data, respectively. Please see the Supplementary material-II for the description of the output tables and figures generated by ncappc.

In the presence of the simulated data obtained using of the concerned PopPK model, *ncappc* function estimates the same set of NCA metrics from each set of the simulations. Next, the function performs the individual and population level diagnostic tests and produces a complete report with the graphical and tabular outputs reporting the individual and population level diagnostic results involving simulation mean, deviation from the observed value and Normalized Prediction Distribution Error (NPDE) values of each NCA metric. All tables produced by *ncappc* are in tab-separated text format and can be easily loaded in generic data visualization software like Excel, R, etc.

2.2. Simulation-based PopPK model evaluation in ncappc package

The objective of this feature of the *ncappc* package is to perform a PopPK model evaluation using simulation-based diagnostics by comparing the NCA metrics estimated from the simulated data with the same metrics estimated from the observed data.