A Pharmacokinetic Program (*PKfit*) for *R*

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Introduction: *R* (www.r-project.org) is a language and an integrated suite of software facilities for data manipulation, calculation, and graphic display. It is also an environment within which many classical and modern statistical techniques have been implemented. *R* is also a freeware under GNU license. Since many developers have created many packages for *R*, *R* now has been included many powerful packages for statistics and numerical analysis. Therefore, the purpose of this study was to create a nonlinear regression (including a genetic algorithm) program (*R* script) to deal with data fitting for pharmacokinetics (PK) in *R* environment using its available packages. We call this tool as *PKfit*. Results obtained from *PKfit* will be compared with other two available PK programs, *WinNonlin* (www.pharsight.com) and *Boomer* (www.boomer.org). **Methods and Materials**: We used *lsoda* function (in *odesolve* package) to solve all differential equations used to define PK models. As for data fitting algorithms, *PKfit* included Gauss-Newton algorithm (*nls* function in *stats* package) for non-linear regression, and the Nelder-Mead simplex method (*optim* function in *stats* package) for minimization of weighted sum of square (WSS), as well as the genetic algorithm (*genoud* function in *rgenoud* package). Design goal of this tool was aimed to be easy-to-use and powerful, so a menu-driven interface was developed. Users just follow the menu step by step and will get the job done. Different pharmacokinetic models (intravenous drug administrations with i.v. bolus or i.v. infusion, extravascular drug administrations, linear (1^{st}-order absorption/elimination) or nonlinear (Michaelis-Menten model)) were all considered and built for *PKfit*. Two weighting schemes, 1/Cp(obs), and $1/Cp^2$(obs) were also built in *PKfit*. The output includes a summarized table (consisting of time, observed and calculated concentrations, weighted residuals, area under plasma concentration curve (AUC), and area under the first moment (AUMC)), goodness-of-fit, final PK parameter values, and diagnostic plots for *nls* such as linear plot, semi-log plot, and residual plot. **Results and Discussion**: We have successfully built *PKfit* package written in R script. *PKfit* provides two major functions: normal fitting and simulation. With only a few examples, most results obtained from in *PKfit* were comparable to those obtained from *WinNonlin* or *Boomer*. **Conclusion and Future Work**: *PKfit* running on *R* has been built and has been proved its efficiency in data fitting functions. We may need to consider to improve the stability of *PKfit*, and add Monte-Carlo simulation for *PKfit* in the future. [Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.]

Keywords: *R*, Pharmacokinetics, Nonlinear Regression, Data Fitting, Modeling, Simulation