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# A COMPARISON OF COMPUTATIONAL APPROACHES TO THE POPULATION PHARMACOKINETICS. AN EXAMPLE OF TOXICOLOGICAL DATA

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**Abstract:** Four different approaches to population pharmacokinetic analysis were applied to routine clinical data on carbamazepine intoxications in epileptic and alcoholic patients. The computational issues were noticed for maximum likelihood based methods, while Markov Chain Monte Carlo approach revealed that the estimates of absorption and lag parameters might be unreliable. Non-identifiability of these parameters may be the source of computational problems with other methods. Simultaneous use of different approaches to population pharmacokinetics is therefore advised, since it allows for verification of the obtained results.

**Keywords**: population pharmacokinetics, statistical estimation, maximum likelihood, expectation-maximization, Markov chain, Monte Carlo, carbamazepine, epilepsy, alcoholism

**Abbreviations:** CBZ – carbamazepine, EM – expectation-maximization, MCMC – Markov Chain Monte Carlo, PK – pharmacokinetic, PPK – population pharmacokinetics, TDM – therapeutic drug monitoring

Population pharmacokinetics (PPK) tries to find a model, which describes a drug course in the patient's body and investigates statistical distribution of parameters of that model in the population under study. The purpose of this analysis may be purely utilitarian (e.g. in therapeutic drug monitoring, TDM) or cognitive (as one may wish to do with the data gathered during clinical observation).

The statistical theory makes parameter estimation possible also in the case of sparse data, i.e. when the number of measured drug concentrations from a given subject is less than or not much greater than the number of pharmacokinetic (PK) model parameters. This is of great advantage, because it makes routine clinical data usable for population analysis. However, an estimation of the model for sparse data is a very difficult statistical and computational task. A number of approaches to this problem have been developed. Table 1 enumerates the most important of them along with the appropriate computer programs.

Each of these methods constitutes significantly distinct approach to the PPK problem, both in the aspect of the assumptions as well as numeric algorithms applied. The first three approaches have their origins in the maximum likelihood method, the very fundamental statistical principle.

The NONMEM program searches for a likelihood function maximum by means of numerical algorithms. Next two methods search for likelihood maximizing parameters without necessity of explicit calculation of likelihood function. These methods differ in the way they express the parameter distribution. In the parametric EM, the parametric family of distributions (like normal or log-normal) is assumed. On the other hand, the non-parametric EM replaces continuous statistical distributions by their discrete approximations (3, 5). This allows for a greater flexibility in a description of parameter distributions.

The principle of the MCMC approach is quite different. It makes use of statistical experiment in order to determine empirical distribution of each measurable population characteristic under investigation (6, 7).

It was of interest to investigate, for the approaches considered:

- to which degree estimated parameters agree with their true values,
- to evaluate the efficacy of the

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approaches/programs and the agreement of the results between them.

The first point was the subject of previous simulation studies (8, 9), in which the true parameter values where known and it was possible to control a fulfillment of the assumptions.

In the present study, a focus is on the real clinical data. Not only PK parameters true values remain unknown, but also one does not know to which degree assumptions of the respective methods are correct.

## MATERIAL AND METHOD

Patients and samples

Patient records with evidence of CBZ intoxication from the Clinic of Toxicology, Jagiellonian University, Collegium Medicum were used. There were selected patients belonging to the following groups:

- epileptic patients (E),
- patients with alcoholism with alcohol detected in their blood at the time of admission to the hospital (A),
- patients with alcoholism with no alcohol in blood at the time of admission (N).

Each patient had CBZ concentration determined at the time of admission, and the additional 0-4 concentrations measured in the course of therapy (Figure 1). Thus, the data are sparse. It is unknown what CBZ form was taken. In addition, the suppositions on the time and dose of CBZ administration are only rough approximations.

Pharmacokinetic and statistical model

The clinical observations made in the course of routine medical care suggest the CBZ pharmacokinetics for therapeutic doses may be described by the one-compartment model with the first order elimination (10). Due to the lack of data on the drug form administered, both zero and first order absorption had to be considered. In the case of the zero order absorption – which may be adequate for the prolonged release drug forms – the time of absorption was chosen as a pharmacokinetic parameter. For the first order absorption, the related PK parameter is the first order absorption constant, . There is also a parameter  in both models, which combines the lag time with the correction for the time of administration.

The volume of distribution could not be selected as the model parameter because of the uncertainty of the drug form and its dose. Therefore, the parameter is a mixture of the volume of distribution, the fraction absorbed and the correction of dose to its true value. The clearance is the fourth parameter of the model. Unfortunately, important patient data, such as body weight or height, were missed. It made investigation of regression models for clearance and parameter unfeasible.

The Gaussian distribution was assumed for parameter in the studied populations. For the other parameters log-normal distribution was assumed. The intraindividual variability of the measured concentrations was assumed to be normally distributed with a heteroschedastic variance model (the constant coefficient of variance model).

## RESULTS AND DISCUSSION

Computational issues

The computations with the NONMEM program were not fully successful for any group and model. Despite the estimates of the PK parameters and their variances were obtained, the estimation of the results accuracy failed and the software notified the numerical issues. For a certain initial data, the program unexpectedly exited without any message. The choice of proper initial parameter values was the main difficulty in the computations with NONMEM.

Thermo Kinetica was less sensitive on initial parameters, but the stop criterion for iterations appeared to be too liberal: using the final parameter values as initial values for the next run sometimes led to significantly different final results and each run the results were different.

The simulation studies yielded promising results for the NPAG program (8). Unfortunately, it

Table 1. Methods and software for population pharmacokinetic analysis of sparse data.

| Method | Program | Authors/originators |
|---|---|---|
| Nonlinear mixed-effect modelling | NONMEM (1) | Sheiner L., Beal S. (UCSF) |
| Expectation maximization (EM) | Thermo Kinetica (2) | Mentré F., Gomeni R. |
| Nonparametric EM | NPAG (3) | Jelliffe R., Schumitzky A., Leary R. (USC) |
| Markov Chain Monte Carlo (MCMC) | WinBugs/PKBugs (4) | Lunn D.J., St Mary's Hospital, London |

Table 2. Clearance and absorption parameter estimates for studied programs and both absorption models.

| First-order absorption | | Patient group[1] | | |
|---|---|---|---|---|
| | Program | E (n = 76)[2] | N (n = 35) | A (n = 46) |
| Clearance [L h$^{-1}$] | NONMEM | 5.75 ± 8.52[3] | 8.45 ± 18.44 | 2.17 ± 2.14 |
| | Thermo Kinetica | 4.06 ± 0.70 | 4.64 ± 0.74 | 2.17 ± 1.14 |
| | NPAG | 4.76 ± 2.81 | 5.54 ± 3.10 | 4.41 ± 2.60 |
| | PKBugs | 5.28 ± 4.71 | 6.21 ± 6.04 | 3.70 ± 3.72 |
| Absorption constant $k_a$ [h$^{-1}$] | NONMEM | 0.70 ± 0.007 | 8.42 ± 0.08 | 7.70 ± 0.07 |
| | Thermo Kinetica | 3.58 ± 0.70 | 4.60 ± 1.55 | 14.56 ± 0.94 |
| | NPAG | 3.74 ± 3.93 | 4.61 ± 2.73 | 5.60 ± 8.26 |
| | PKBugs | 11.06 ± 4.20 | 8.90 ± 5.96 | 28.21 ± 20.29 |
| Zero-order absorption | | | | |
| Clearance [L h$^{-1}$] | NONMEM | 6.16 ± 3.90 | 2.22 ± 0.84 | 1.83 ± 0.88 |
| | Thermo Kinetica | 4.43 ± 1.02 | 4.92 ± 0.94 | 2.31 ± 1.27 |
| | NPAG | 3.33 ± 2.34 | 5.46 ± 2.92 | 5.11 ± 3.32 |
| | PKBugs | 5.29 ± 4.72 | 5.77 ± 5.56 | 3.61 ± 3.51 |
| Absorption time [h] | NONMEM | 0.30 ± 0.19 | 0.17 ± 0.15 | 0.18 ± 0.15 |
| | Thermo Kinetica | 2.68 ± 0.97 | 1.93 ± 0.57 | 1.94 ± 0.49 |
| | NPAG | 5.22 ± 2.99 | 5.98 ± 4.06 | 9.93 ± 3.68 |
| | PKBugs | 0.72 ± 0.24 | 0.53 ± 0.78 | 0.28 ± 0.13 |

[1] E – epilepsy; N – alcoholism, no alcohol in blood; A – alcoholism, alcohol detected in blood.
[2] Number of subjects in group.
[3] Population parameter value ± its standard deviation in population.

performed worse in the present study. Only the test version (beta) was available to the authors. It is not known, if the program is still under development.

No significant dependency of WinBugs/ PKBugs results on the (reasonably chosen) initial parameter guesses was found. The observed statistical, post-hoc distributions of PK parameters provide a certain insight into the reasons of computational issues encountered with other programs. Figure 2 shows probability density plots for the zero-order absorption model parameters. The distributions for clearance and parameter are in the agreement with the assumed log-normal distribution. On the other hand, the shape of other parameters distribution appears irregular and it changes with the number of iterations. This indicates the estimates of absorption time and of parameter are subject to a greater uncertainty. Nevertheless, the plot suggests short absorption times, not exceeding 2 hours. This is in agreement with the patients' profiles (Figure 1), where, for a majority of subjects, the absorption phase is poorly seen. It may thus be presumed that the prolonged release drug forms were rarely used. Consequently, the use of the first order absorption model as a population model is better motivated. The results of such modelling with a PKBugs program are shown in Figure 3. The clearance and parameter distributions are again regular and similar to those from the previous model. Also remaining two parameters behavior is similar to that previously observed. Therefore, the first order absorption constant and parameter cannot be estimated with a satisfactory accuracy.

In the study described, the comparison of the absorption and elimination parameters is of special interest. Table 2 compiles estimates of these parameters obtained for the subsequent programs and both absorption models. Despite significant differences for the same data sets were obtained, their mutual relations between groups are, in general, consistent. Besides one exception, for each method and absorption model the lowest clearance values were obtained for the A group and the highest values of that parameter for the N group. Contrary, the first order absorption constant seems to reach the highest values in the A group.

The above suppositions require a thorough statistical reasoning before they could be expressed as

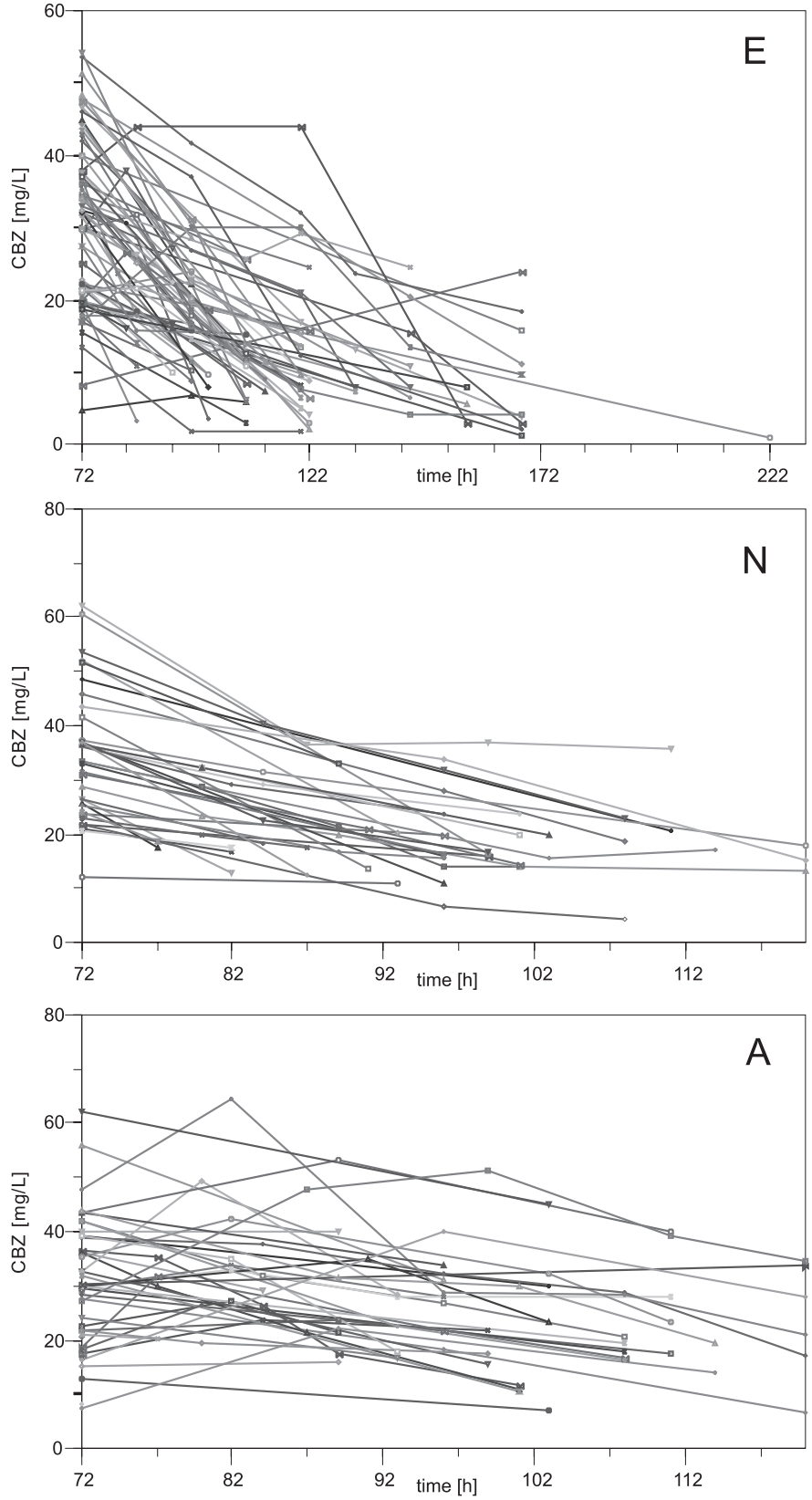


Figure 1. Spaghetti plot of CBZ concentrations in three patient groups. E – epilepsy; N – alcoholism, no alcohol in blood; A – alcoholism, alcohol detected in blood.

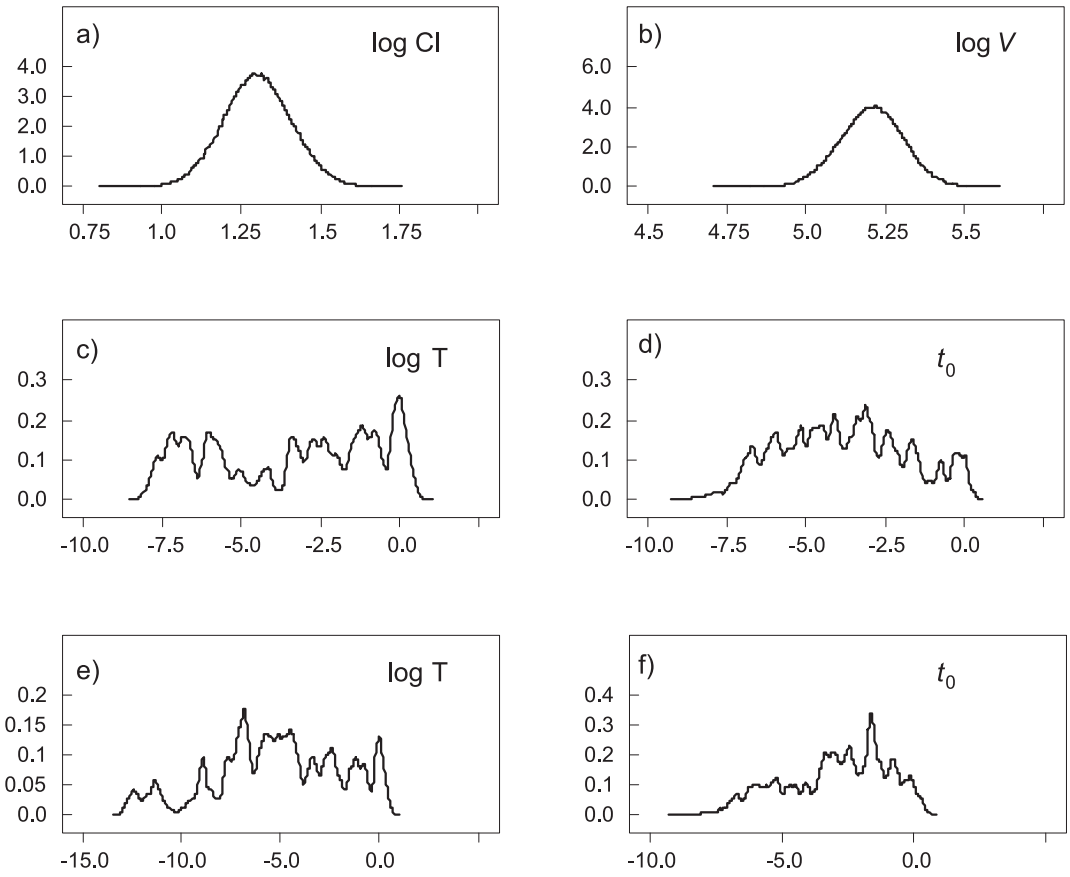


Figure 2. Empirical probability density of PK parameters for the one compartment model with zero order absorption: a – log of clearance, b – log of $V$ parameter, c – log of absorption time, d – $t_0$ parameter, e and f – same as c and d, respectively, but obtained for the random sample twice as large as for a-d (600000 vs 300000).

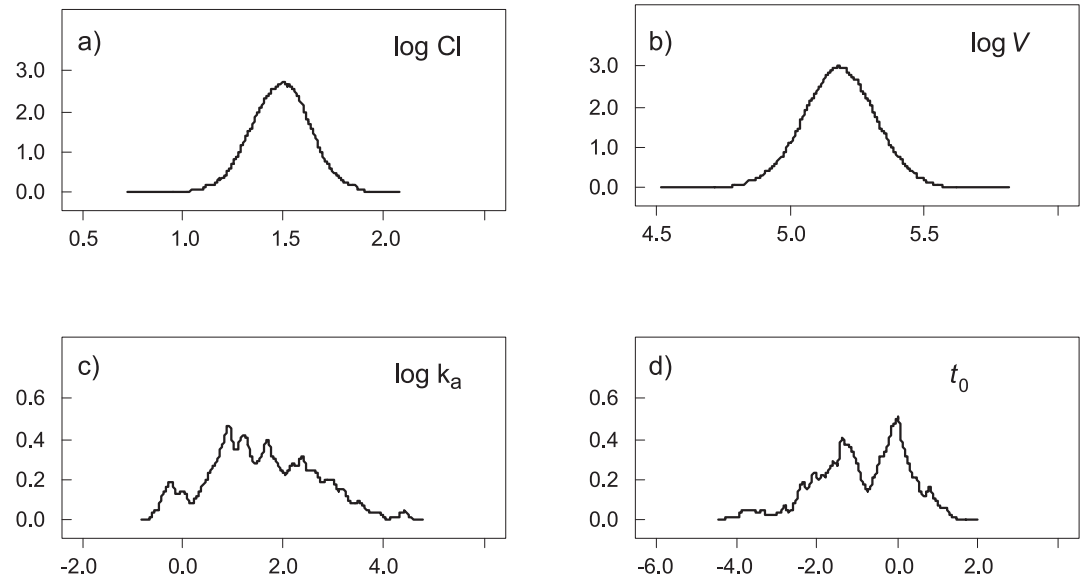


Figure 3. Empirical probability density of PK parameters for the one compartment model with first order absorption: a – log of clearance, b – log of $V$ parameter, c – log of absorption rate constant, d – $t_0$ parameter.

credible conclusions. This might be a subject of a separate study.

## CONCLUSIONS

The computational issues noticed are not necessarily a proof of malfunctioning of the given approach or bugs in a software. Rather, they indicate the assumptions of these approaches do not hold. It is possible, not all the model parameters are identifiable (11). For the majority of profiles the absorption phase is poorly noticeable, therefore one could not expect reliable estimates for parameters related to this process.

Simultaneous use of different approaches to population pharmacokinetics is recommended, because it provides better inspection into possible imperfections of population pharmacokinetic model.

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