Propagation of population pharmacokinetic information using a Bayesian approach

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Objectives

To investigate the propagation of population pharmacokinetic information across different datasets by applying Bayesian techniques. The aim is to summarize the population pharmacokinetic estimates of a dataset in appropriate statistical distributions in order to use them as Bayesian priors in consequent population pharmacokinetic analyses. The main task of this study is to compare results obtained by such analyses with the respective meta-analysis of the entire data.

Methods

Various data sets of simulated and real data (Table) were fitted with WinBUGS, with and without informative priors. Namely, the posterior estimates of fittings with non-informative priors were used to build informative priors and the whole procedure was carried on in a consecutive manner. The estimates of fittings with informative priors where compared with meta-analysis fittings of the respective combinations of data sets. Intuitively one would expect identical results between the two methods, even in the case of non-exchangeable populations. However, the posterior distributions have to be summarized parametrically in order to be used as priors. This introduces assumptions for the parametric form of the posterior distributions and the correlations between them which are only approximate, because of the nonlinearity of the model. So, some information may be lost there.

Data

Four groups of datasets were utilized. Group A consists of 5 dense datasets (d3, d6, d12, d24, d48) each one of them including 3, 6, 12, 24 and 48 individuals, respectively, and one sparse dataset (s48) of 48 individuals. These data sets were simulated using a one compartment model with first order input and the same parameter values throughout. Group B consists of 2 datasets (b1, b2) with the same characteristics as d12 of group A, but this time the two datasets had different mean values for clearance (CL), to produce different populations. Group C consists of 3 datasets (r1, r2, r3) of 14 rats each, administered with midazolam. The datasets came out of two studies of 20 and 22 rats, respectively, (Aarons et al 1991, Mandema et al 1992) after shuffling the individuals to achieve homogeneous population. Group D consists of 3 datasets (d202, d229, d239) of healthy volunteers administered with defetilide, orally (Nam 2003).

group	A						B		C			D		
dataset	d3	d6	d12	d24	d48	s48	b1	b2	r1	r2	r3	d202	d229	d239
comment	homogenous population						shifted CL to achieve non-homogeneity		shuffled to achieve homogeneity			non-homogeneous population		
drug	Simulated								midazolam			dofetilide		
species									rats			humans		
admin	first order input								iv, zero order infusion			zero order, oral absorption with lag time		
model	One-compartment								two-compartment			one-compartment		
parameters	CL, V, Ka								CL, Q, V1, V2			CL, V, Tlag, Tinf		
number of subjects	3	6	12	24	48	48	12		14			10	25	18
number of measurements per subject	17					2	17		~13 single			~32 single	~72 multi	~51 multi

Analysis

The analysis of the data was performed with WinBUGS. For group A, one compartment pharmacokinetic model with first order absorption was used with 3 parameters, namely, clearance (CL), volume of distribution (V) and absorption rate constant (Ka). A general three-stage hierarchical model was followed:

model $y_{ij}= f(\theta_i,x_{ij})+\varepsilon_{ij}$

1st stage $\varepsilon_{ij}\sim N(0,\tau^{-1})$

2nd stage $\theta_i\sim N_p(\mu,\Omega)$

3rd stage (priors) $\tau\sim\Gamma(a,b)$, $\mu\sim N_2(m,p^{-1})$, $\Omega^{-1}\sim W(S,v)$

Where f is the nonlinear model, y_{ij} is the logarithm of the jth observation of the ith individual at observation point x_{ij}; θ_i is a vector of the logarithms of the model parameters for the ith individual; ε_{ij} is a proportional residual error (because the model is on a log scale); N, N_2, Γ and W are the normal, 3D multivariate normal, gamma and Wishart distributions, respectively; τ is the residual error expressed as precision; μ is a vector of the mean values of the distribution of the θs; Ω is the interindividual variability matrix, a and b are the gamma distribution parameters for the uncertainty of τ; m and p are the mean value vector and precision matrix of the uncertainty distribution of μ, respectively, and S and v are the scale matrix and degrees of freedom, respectively, of the Wishart distribution for the uncertainty of the Ω matrix.

The procedure followed was the following:

1. Each dense set was fitted with non-informative priors.

   $m=m_0$, $p=10^{-4}$,
   $S=(\Omega_0 \cdot v)^{-1}$, $v=3$,
   $a=0.001$, $b=0.001$

2. The output samples from posterior distribution from this fitting was then used to construct appropriate priors.

   $m=\text{mean}(\mu_{post})$, $p=\text{var}(\mu_{post})$,
   $S=\text{mean}(\Omega^{-1}_{post})/v$, $v=\text{int}(2\cdot\text{mean}(\Omega^{-1}_{post})_{11}^2/\text{var}(\Omega^{-1}_{post})_{11}))$,
   $a=\text{mean}(\tau_{post})^2/\text{var}(\tau_{post})$, $b=\text{mean}(\tau_{post})/\text{var}(\tau_{post})$

3. The sparse data set was fitted with these informative priors.

4. The combined datasets of the sparse data together with each one of the dense datasets were fitted using non-informative priors (as before).

5. The samples from the posterior distributions of steps 3 and 4 where compared by sorting the 2 chains and plotting them against each other, together with the identity line which is considered to be the reference point. (Fig. 1) Ideally if the two distributions are identical, their samples are plotted exactly on the identity line.

Fig 1

A schematic example of the comparison of two chains. The red line is the identity line.

Chain α	Chain β
α_1	β_1
α_2	β_2
α_3	β_3
α_4	β_4
α_5	β_5

The notation A(B) means that dataset A was fitted with prior B, while A&B stands for meta-analysis fitting of datasets A and B.

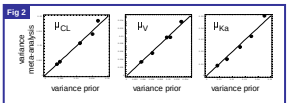
The analysis was similar for the other datasets. For group B, the analysis was identical to group A and for group C, 4 parameters were used instead of 3, i.e. clearance (CL), intercompartmental clearance (Q), central volume (V1) and peripheral volume (V2). In group D a one-compartment model was used instead of the established for dofetilide two-compartment, because the oral phase masked the fist kinetic phase. So, 4 parameters were used again, CL, V, lag time (Tlag) and infusion time (Tinf), but also the random effects matrix was partitioned to a 2x2 matrix including CL and V, and two separate variance elements for Tlag and Tinf.

Results

Homogeneous simulated data (group A)

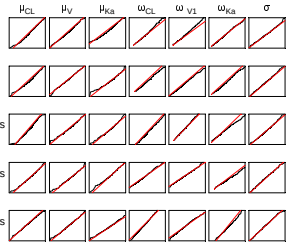
In group A, 5 simulated, dense datasets containing progressively larger number of subjects, hence more information, were used as priors to fit a sparse dataset of the same population, in two different ways. First, each one of the dense datasets was fitted separately with WinBUGS and the posterior distributions were used as priors in a WinBUGS fitting of the sparse dataset. The results of the latter is compared to a meta-analysis WinBUGS fitting of each one of the dense datasets together with the sparse dataset, combined.

Fig 2



The two results are compared, plotting the variances of the distributions of the 3 mean population pharmacokinetic parameters, i.e. μ_{CL}, μ_V and μ_{Ka}, which are actually measures of the uncertainty of the estimates for these parameters. One can see clearly the following: (a) The more the information used (more individuals in the dense data), the smaller the variances (less uncertainty) of the distributions are, for both methods (from top-right towards bottom-left corner), a result which is very reasonable and anticipated. (b) The variances of the both methods are of the same magnitude, making the points to lie very close to the identity line, which is also drawn.

Fig 3



Direct comparison (see Fig. 1) of a few thousand samples from the two distributions, reveals that they are identical in almost all cases. So in group A, where the population is homogeneous, the conclusion is that the two methods, prior and meta-analysis give the same results.

Non-homogeneous simulated data (group B)

In group B, two datasets with the same amount of information, but with difference in one of the population parameters (CL) were fitted by the two methods as with group A, and compared in the same way.

Fig 4

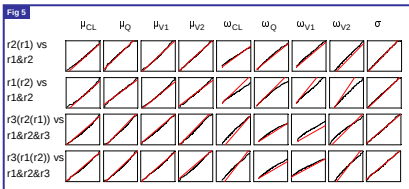
A direct comparison of the posterior distributions of the two methods reveals that the distributions are not at all the same. So in this case, where the populations are not exchangeable, the two methods do not give the same results, although intuitively one would expect the opposite.

This may be due to the way the prior distributions are generated from the respective posterior distributions. When the priors are set up, parametric representations are generated where μ, Ω and σ are considered independent and correlations between them are ignored. However, because the model is nonlinear this assumption is not accurate, a fact that is attenuated when the population is not homogeneous.

Rat data (group C)

Group C is an application of the approach in real rat data. Two homogeneous datasets were fitted as before, but this time a second step was performed as well, allowing the posterior of these fits to be used as a prior to fit a third dataset. Thus the information, included in the prior, is considered to propagate one more step, and is tested against the meta-analysis of the three datasets, combined.

Fig 5



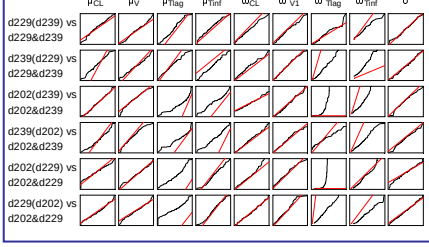
The direct comparison of the distributions of the prior method and the meta-analysis approach, reveals that the compared distributions are identical for the mean value population parameters and the residual error, and are not identical but are not that different in the interindividual variability parameters. The latter could be due to the relative small number of individuals in each dataset, being 14.

The conclusion here is a Bayesian prior can summarize very well real experimental data, when these are homogeneous.

Human data (group D)

In group D the method was applied to real human data. Three datasets were fitted every two as before, with the prior and meta-analysis methods, producing six sets of results.

Fig 6



The direct comparison of the posterior distributions coming from the two methods shows that the although it does not fail completely, it does not perform as well as with the rat data where the data were very homogeneous. Also, the data exhibit large variability in the absorption phase which is depicted in the total failure of the comparison for the respective interidividual parameters Tlag and Tinf, a fact that may have played an important role in this generally moderate performance.

Conclusions

From the results presented above, it is clear that population pharmacokinetic information can be summarized in Bayesian prior distributions that can be used consecutively with other analyses. The procedure is an alternative to the meta-analysis and gives comparable results, which are almost identical when the data utilized are homogeneous enough. The prior method has the advantage over the meta-analysis method, that it can be applied when the data used for prior information are not actually available. Another advantage of the prior method compared to the meta-analysis method is the smaller computational time required for the former. This comes from the fact less data are used in the prior method, because part of the information is included in the prior, unlike the meta-analysis method where all the information is included in the data.

References

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