A population pharmacokinetic model for S-warfarin: application of a mixture model to determine genotype/phenotype

Ivan Matthews and Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK

Introduction

Mixture models are useful in population pharmacokinetics and pharmacodynamics to characterise underlying population distributions (2 or more subpopulations) that are not adequately explained by the evaluated covariates. When applied in NONMEM, the subpopulation, to which an individual was classified, can be determined by viewing the post-hoc Bayesian estimates. Polymorphic metabolising enzymes, such as those from the cytochrome P450 (CYP) family, may give rise to a multimodal clearance distribution. Their involvement in the elimination of many drugs means that the use of mixture modelling may become common in order to categorise phenotype/genotype. Several common drugs such as warfarin, metoprolol, ibuprofen, and phenytoin are eliminated via a polymorphic enzyme pathway.

The vitamin K antagonist warfarin is an important drug in the treatment of thromboembolic disorders. The response of individuals to warfarin has been shown to vary widely. The polymorphic enzyme CYP2C9 is largely responsible for S-warfarin metabolism. The allelic variants CYP2C9*2 and CYP2C9*3 are associated with reduced activity and increased risk of haemorrhage especially at the initiation of therapy.

Objectives

1. Predict the extent to which CYP2C9 polymorphisms alter the pharmacokinetics of warfarin.
2. Demonstrate whether NONMEM can be used to correctly predict the genotype or phenotype of an individual using a mixture model.

Materials and Methods

Study Design

Simcyp® version 5 was used to generate a virtual population of 100 patients and their individual pharmacokinetic profiles. A random error component of 10% was added using S-plus. Each virtual patient received 10mg of S-warfarin orally once a day for 7 days. With pharmacokinetic profiles taken on days 1 and 7. The virtual patient demographics are given in Table I.

Table I – Patient Demographics

	Mean	Range
Poor metaboliser phenotype	5%	
Sex	50% Male	
Age (years)	50	20 - 80
Weight (kg)	75	49 - 114

Pharmacokinetic Analysis

A one compartment first order absorption pharmacokinetic model was fitted to the data using the ADVAN2 TRANS2 subroutine from the NONMEM library. An allometric weight model was applied to standardise volume of distribution (V) and clearance (CL) using a standard weight (WT_{STD}) of 70 kg. In order to detect the polymorphism a mixture model with two clearance subpopulations corresponding to a phenotype of poor (PM) and extensive metabolisers (EM) was tested, where PMs are carriers of the CYP2C9*2 or *3 alleles. The results were then compared to a categorical model which uses the phenotypic data provided by Simcyp® as a covariate.

Clearance Model

$$CL_i = CL_{GRP} \cdot e^{PPV_{CL_i}}$$

$$CL_{GRP} = CL \cdot F_{WT_{CL}} \cdot F_{CYP_{CL}}$$

$$F_{WT_{CL}} = \left(\frac{WT}{WT_{STD}}\right)^{3/4}$$

$$\text{If pheno} = 2 \text{ then (PM)}$$

$$F_{CYP_{CL}} = \theta$$

$$\text{Else (EM)}$$

$$F_{CYP_{CL}} = 1$$

PPV_{CLi} was assumed to be a normally distributed random variable with mean 0

CL_{GRP} is the covariate predicted group value for Clearance

CL_i is the individual Clearance for the i^{th} patient

Volume Model

$$V_i = V \cdot F_{WT_V} \cdot e^{PPV_{V_i}}$$

$$F_{WT_V} = \frac{WT}{WT_{STD}}$$

PPV_{Vi} was assumed to be a normally distributed random variable with mean 0

V_i is the individual volume for the i^{th} patient.

Error Model

$$Y = F \cdot e^{ERR(1)} + ERR(2)$$

F is the predicted warfarin concentration (without residual error)

Y is the individual prediction including a proportional (ERR(1)) and additive (ERR(2)) residual error component

ERR(1) and ERR(2) were assumed to be normally distributed random variables with means of 0

In the case of the mixture model pheno is the NONMEM parameter MIXNUM. MIXNUM is the index of the subpopulation for which variables are to be computed. The estimate of the subpopulation to which an individual belongs is given by MIXEST. The fraction belonging to each subpopulation is estimated where P(1) is the fraction of the population in the 1st subpopulation and the sum of P(1) and P(2) equals 1. For the categorical model (final model) pheno is given by the phenotype covariate in the data file.

Computation

Model building was performed using NONMEM version V release 1.1 (NONMEM Project Group, University of California, San Francisco, CA, USA) under MS-DOS on a Pentium 4 3GHz PC using Microsoft windows XP and the g77 FORTRAN compiler. All model building was performed using the first order conditional estimation method with the interaction estimation option.

Results

Pharmacokinetic analysis

When covariate models were applied, weight was found to be a significant covariate for the clearance and volume of distribution parameters. No significant age effect could be demonstrated on clearance or volume of distribution parameters after weight had been taken into account, as demonstrated by the marginal drop in objective function value (Table II).

Table II – Model Building

Model	Description	Objective function value	No. of Structural Parameters
Base 1 comp	No covariates	-14789	3
1 comp	Age on CL	-14789	4
1 comp	F_{CYP} on CL	-14799	4
1 comp	Weight on V & CL	-14818	3
1 comp Mix	Weight on V & CL, 2 subpopulations	-14820	5
1 comp Cat*	Weight on V & CL, F_{CYP} on CL	-14831	4

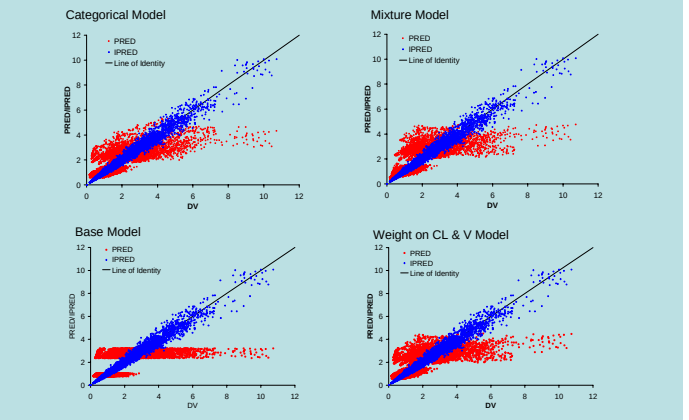
* Final Model

Table III –Parameter Estimates for final model and the mixture model

	Categorical Model				Mixture Model			
Parameter	Estimate (95%CI)		BSV*1 (SE(CV)*2)		Estimate (95%CI)		BSV*1 (SE(CV)*2)	
Ka	1.66	(1.54-1.78)	0.305	(0.166)	1.66	(1.54-1.78)	0.305	(0.166)
CL ($L.h^{-1}.70kg^{-1}$)	0.139	(0.122-0.156)	0.602	(0.12)	0.12	(0.038-0.202)	0.567	(0.12)
V ($L.70kg^{-1}$)	8.75	(8.14-9.36)	0.346	(0.15)	8.75	(8.14-9.36)	0.346	(0.519)
F_{CYP}	0.36	(0.2-0.52)			2.93	(-6.05-11.9)		
Proportional error	0.101	(0.021)*3			0.101	(0.021)*3		
Additive error	Minimal				Minimal			

*1 BSV expressed as an approximate CV, *2 SE expressed as a CV of the BSV term, *3 SE expressed as a CV of the proportional/additive error

Fig. 1 Population and individual predicted warfarin concentrations vs. measured, for 4 different models



Bayesian post-hoc subpopulation classification

The mixture model was not able to assign any of the PMs to the appropriate group. When constrained, the value of the fractional covariate effect of CYP2C9 (F_{CYP}) on clearance tended towards 1 (no effect) and also an under prediction of the mixing proportion (no PMs). When left unconstrained the value of F_{CYP} exceeded 1 creating an unidentified (by the CYP2C9 covariate data) group of ultra high metabolisers. Despite this the fit and population parameter estimates of the mixture model were similar to those of the categorical model except for the value of F_{CYP}.

Discussion

Mixture models are not necessarily only applicable to biologically known subpopulations such as poor and extensive metabolisers, but can also be applied as a purely statistical approach. In the above example it is clear that a few individuals with high CL were found to be a more significant factor than those with very low CL even though this new subpopulation has not been described. Further work should be done to evaluate the factors that influence the mixture model and then to quantify these.

The final model was still not able to significantly reduce the between subject variability in clearance. Previous studies have shown that even when covariates can explain 60% of between subject variability, patients may still not receive safe and effective therapy, necessitating the use of a therapeutic drug monitoring approach to dosing.

Conclusions

A one compartment first order absorption pharmacokinetic model with a covariate effect of weight on volume and clearance and a fractional effect of CYP2C9 on clearance was an adequate model to describe the data.

The mixture model was not efficient at assigning the appropriate phenotype to the patients.

Reference

www.simcyp.com

Ivan.Matthews@postgrad.manchester.ac.uk