Determination of PK parameters

Mixed-effects population models were fitted to the log-transformed propofol blood and plasma concentration versus time data. The program NONMEM version 6 was used. Models were fitted using the first order conditional estimation method with interaction between the interindividual error terms (ETAs) and the random residual error term allowed. Random residual error was described using an additive error model. A Compaq Digital FORTRAN V6.6 compiler was used with an Intel vPro 1.9GHz CPU (Intel, Santa Clara, USA) under Microsoft Windows XP Professional (Microsoft, Seattle, WA, USA). The data were first applied to two- and three-compartment mamillary models. A two-compartment model provided the best description of the basic model structure. This model was developed by adding ETA parameters to each structural parameter until no further model improvement could be justified, according to the goodness-of-fit criteria described below. A proportional variance model was used to describe the inter-individual variability.

Using the output from the basic model, scatter plots were constructed so that the distribution of the ETA parameter estimates (reflecting inter-individual variability) and the structural model parameters estimates (clearances and volumes) with the potential model covariates i.e. animal body weight, sample matrix and propofol formulation, could be examined. Where these plots suggested an influence of the covariate on propofol pharmacokinetic parameter estimates, we then examined models which allowed the structural pharmacokinetic parameters to differ with covariates. Sample matrix (blood vs. plasma) was examined as a dichotomous covariate. Hence, in models evaluating the influence of sample matrix, the pharmacokinetic parameters were allowed to assume different values in animals from which blood was assayed, relative to animals from which plasma was assayed. Formulation was examined as a dichotomous covariate (Diprivan vs. PPF-PM (all types)) and also as a categorical variable with four groups (Diprivan, PPF-PM 7%, PPF-PM 10%, PPF-PM 12%). If the influence of formulation was being investigated on a pharmacokinetic parameter which had already been assigned an effect of sample matrix, then the potential influence of propofol formulation was tested in both plasma and blood groups separately and also on all groups (blood and plasma groups combined). The statistical significance of each proposed covariate-parameter relationship and the requirement for ETA parameters was assessed using the likelihood ratio test (where appropriate i.e. for nested models) and by consideration of the Akaike Information Criterion (non-nested models) and the precision of the final parameter estimates (all models). For nested models, the justification for each additional effect was for it to improve the goodness-of-fit statistic (-2
log likelihood) by more than 6.6 (evaluated against the chi-square distribution, this is equivalent to 
significance at the 0.01 level). The improvement (or lack of) in model goodness-of-fit was also 
assessed visually by the examination of diagnostic plots. After completing the model build, the 
necessity for each added component was re-assessed by removing it from the model and evaluating 
the resulting impact on the model fit. If the removed component caused an increase in the goodness-
of-fit statistic equivalent to significance at the 0.005 level (i.e. the removal of the component 
significantly worsened the model), it was allowed to remain.