Population pharmacokinetics in anesthesia

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Predicting the course of drug concentration and drug effect in an individual patient is the major goal of clinical pharmacology. To provide a description of the time course of the concentration and effect after drug administration, pharmacokinetic (PK) and pharma- codynamic (PD) modelling are used. Intravenous anaesthesia is particularly concerned with an understanding of the time course of the concentration and drug effect. Although physiology-based pharma- cokinetic modelling is currently widely used in drug development, mammillary models are more suitable and still widely employed in anesthesiologic research. However, these methods give only a general approximation of the PK and PD of a drug without exploring the factors influencing inter-patient variability and dose–response relationship.

In the late 1970s, Lewis Sheiner and co-workers described a new approach to pharmacokinetic data analyses, which was later called'population pharmacokinetics'. Population PK or PD is the study of the variability in drug concentration or pharmacological effect between individuals after standard dosing regimens are applied. Variability between patients can be described and the sources of this variability can be identified. Unexplained inter- and intra-individual variability can be modelled, even when the design of data collection varies considerably between individuals. It also enables parameter estimates to be obtained even for those individuals for whom there are too few observations to allow parameter estimation by alternative standard methods. The latter is important when concerning the lack of study of medications in paediatric patients. The use of population PK analysis and accompanied simulation is essential for applying phar- macokinetics in newborns and small children. In conclusion, population modelling provides a powerful tool to explore factors that influence inter-patient variability in the dose–response relationship and can be applied to develop optimal dosing strategies and a more efficient drug development programme.

Population based PK/PD analysis has greatly improved the efficiency of PK/PD analysis. Various techniques are available to perform population pharmacokinetic-pharmacodynamic data analy- ses. These techniques call for complex, computer intensive calcu- lation and statistical methods and its use increased exponentially recently after the development of powerful microprocessors. The statistical technique used in population pharmacokinetics is called nonlinear mixed effects modelling. The word 'mixed' refers to fixed and random effects. An example of a fixed effect is an increased sensitivity to the effect of drug in the elderly. Random effects refer to the inter-individual and residual sources of variation. The parameter values for an individual patient will differ from the expected values because of inter-individual variability. Residual variation includes intra-individual and inter-occasion variability, measurement error and model misspecification errors. Residual error arises because of the model estimated values are oversimplifications of reality.

Population PK/PD modelling has contributed substantially to the practise of intravenous anaesthesia and first population PK articles in anaesthesiology emerged more than 20 years ago. Several studies have been published and typical anaesthesiological endpoints, such as level of consciousness and analgesia have been modelled. During the last 10 years several aspects of the PK and PD of anesthetics has been revealed with population approach.