THE CONCEPT OF PK MODEL BASED DRUG ADMINISTRATION (TCI)

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With a pharmacokinetic model the time course of the plasma concentration can be described and predicted based on a given drug input. These parameters can be used in Target controlled infusion systems for controlling the infusion rate. For several reasons the first commercially available TCI system was designed to control the plasma concentration - that is, the target was the plasma concentration.

In clinical practice the anesthesiologist attempts to reach the drug effect as fast as possible not only during induction but also during the course of an anesthestic if more drug effect is required. It is common sense that the drug has to move to an effect site before it can exert its intrinsic effect. It is also obvious that there is some time delay between the time course of the plasma concentration and the time course of some (hypothetical) concentration at this effect site. Based on this observation in data of the muscle relaxant Pancuronium, in 1978 Hull et. al.1 introduced the idea of a biophase compartment. With this additional compartment they attempted to account for this observed time lag between the time course of plasma concentration and the effect. Because this compartment was treated as a „true“ compartment the parameters of the pharmacokinetic description had to be recalculated. Contemporarily Sheiner et.al.2 also used an effect compartment for modeling the effect of d-tubocurarine.

With their concept only one additional parameter (ke0) was used for describing the time course of the effect site concentration. Therefore with 7 parameters, the time course of the effect site concentration can be described for a drug with 3 compartment pharmacokinetic characteristic. This model for the effect site is also called the link model because it links the time course of the plasma concentration with the model for the concentration effect relationship.

It is desirable to extend the TCI technology from control of plasma concentration to control of effect site concentration. Therefore, if for such a system a well-established pharmacokinetic model is available, it is tempting to combine this model with a good link model (ke0 value). Unfortunately, if this link model is derived from another study, the ke0 is only valid for the pharmacokinetic parameters derived in the same study. Since the ke0 value eventually is only one of the seven parameters of the overall description of the effect site concentration its applicability is limited to be used together with the other 6 pharmacokinetic parameters. Therefore, using a ke0 value from one study together with pharmacokinetic parameters from another study is unreasonable as e.g. exchanging Cl2 of one parameter set with the one from another experiment.

Time to peak effect site concentration is a unique descriptor of the onset of drug effect.3 The goal of targeting the effect site concentration is to reach the effect as fast possible with no overshoot. This goal is achieved if the TCI system reaches the predicted target concentration at the time of peak effect. Therefore, for combining the pharmacokinetic parameters with pharmacodynamic data of another study, the time to peak effect has to match. It would be only by chance that the combination of the pharmacokinetic parameters with the ke0 of another study will provide with an appropriate time to peak effect site concentration. If one trusts the pharmacodynamic data of a study (that is the tpeak) and wants to combine this information with well-tested pharmacokinetic parameters, a ke0 value can be estimated for this purpose.

For estimating the ke0 value in combined pharmacokinetic-pharmacodynamic a so-called loop-collapsing method can be used. The study most often involves a constant infusion of brief duration until the maximal effect is achieved. The hysteresis between the time course of the measured plasma concentration and the effect is subject to this “collapsing” procedure. Based on the complete model for the effect site concentration, with simulation the time of peak effect site concentration after a bolus dose can be calculated. Experimentally the time to peak effect site concentration can be measured only if a sub maximal bolus dose is given. This measured time on the other hand can then be used to estimate the corresponding ke0 value based on the pharmacokinetic description. Struys et. al.4 used in a study with propofol the measured time of

peak effect from the study of Schnider et. al.5 and combined it with the parameter of Marsh et. al.6 for targeting the effect site concentration successfully.

Time to peak effect (site) concentration is a unique descriptor of the onset of drug effect. Since ke0 values cannot be combined with the pharmacokinetic parameters of other studies, with tpeak it is possible to calculate an appropriate link model for any pharmacokinetic model. This combined model for the effect site is suitable for TCI system.

References

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