Why should I give propofol by TCI? Rationale, utility and questions.

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The concept of TCI (target controlled infusion) is to control the concentration of a drug within a specific compartment of the body. This is termed the 'target concentration', which is achieved by the interplay of complex multi-compartmental models. BUT the basic underlying equation is simple –

Drug concentration = infusion rate (input) / clearance (removal).

As no drug measurement are made during the infusion, the delivery systems are referred to as 'open TCI'. The target level is selected by the anesthesiologist and then adjusted in response to clinical signs to maintain adequate anesthetic depth. When used to induce anesthesia, there is no need for a bolus induction dose as this is included in the machine's calculations when the anesthesiologist sets the initial target concentration.

The principle of TCI was first described as a theoretical approach by Kruger-Thiemer (1968) using a simple two-compartment model. To achieve steady state concentrations, there are three essential components: a loading dose to fill the initial volume of distribution; an infusion to input drug at a rate that matches the loss of drug by clearance; and a super-imposed second infusion to account for the rate at which drug is distributed to the peripheral compartments (tissues) of the body (Vaughan and Tucker, 1975 and 1976). Prior to TCI, the clinician was best able to provide intravenous anesthesia by the combination of a bolus dose and infusion (Boyes et al, 1970) or two differing rate infusions (Wagner et al, 1974), or a combination of the two (Rigg et al, 1981)

The first clinical application of this theoretical model was the CATIA system (computer-assisted total intravenous anaesthesia system) of Schwilden et al (1981). Present algorithms for TCI are usually based on a three compartment kinetic model and the 'target' may be either the blood or plasma concentration, or the effect-site concentration.

A number of different software programs have been developed for TCI - including STANPUMP (from Stanford University); STELPUMP (from the University of Stellenbosch) and RUGLOOP (from Gent University). The first commercial TCI system was the 'Diprifusor System' which was launched in 1996. It is presently available in many countries around the world although not in the USA. The original 'Diprifusor' system contained a microprocessor system that was able to detect the presence of a

single-use pre-filled glass syringe containing propofol. Drug delivery was controlled by the equations shown earlier. With the expiry of the patent for propofol, other cheaper 'generic' forms of the drug have appeared together with second generation TCI delivery systems (termed 'open TCI'). These allow use of a variety of different drugs and drug concentrations, delivered from a variety of different-sized syringes, and implementing a number of different kinetic and dynamic models for propofol. These systems include the Alaris Asena pharmacokinetic System, and the Orchestra Base Primea System. In general, the systems have undergone only limited validation, often using small number studies in ASA I or II patients (although separate model system have been evaluated for paediatric use).

The two main kinetic input programmes for adult use are those attributed to Marsh et al (1991), and Schnider et al (1998). While the former has undergone several predictive studies, there have been no formal studies for the latter. However the advantage of the Schnider model is that it includes two important co-variates besides weight, namely age and lean body mass. For a number of reasons, this may be the better programme for delivering propofol to elderly patients, and for drug delivery if targeting the effect-site.

While the first TCI systems targeted the blood concentration, it was recognised that this was not the site of anaesthetic action, and there were temporal delays between changes in blood concentration and changes in the response of the effect-site (where-ever that is!). The magnitude of this delayed blood-brain equilibrium may be influenced by a number of factors including cardiac output; cerebral blood flow; and the pharmacological properties of the drug including lipid solubility and the degree of ionisation which will influence drug transfer across the blood-brain-barrier. This 'delay' is characterised by the rate constant k_{e0}. The concentration at the effect-site cannot (of course) be measured, but is estimated by surrogates representing the clinical effect of propofol on the brain (ie changes in the EEG, or a derivative thereof).

One of the problems arising from this recognised delay in blood-brain equilibration is that different researchers (using different endpoints) have determined different values for the rate constant – which may depend on the input kinetic model, the age of the patient, the presence or not of significant co-morbidities or intercurrent therapies).

For most systems, there is a lag between changes of the plasma drug concentration and the effect.

This is termed 'hysteresis'. The time for this imbalance between drug concentration and effect is 4.32 x t1/2k_{e0}. For propofol, this equates to about 12 minutes. The greater the value of the rate constant k_{e0} the faster the rate of entry of drug from the blood into the effect compartment and hence the faster the onset of drug effect.

Why use effect-site targeting: as already stated, there is a clear hysteresis between the plasma concentration and clinical effect due to the temporal delay in equilibrium between the plasma concentration and the concentration at the site of action of propofol. However with effect-site targeting, the plasma drug concentration will be increase to an optimal level above the target effect-site concentration (= overshoot). The magnitude of the overshoot depends on the k_{e0} – with a slow k_{e0} requiring greater overshoot in the peak plasma concentration to achieve the necessary blood-effect-site concentration gradient. Obviously this overshoot may result in adverse cardiovascular effects – which are especially relevant in the frail elderly subject and in the presence of dehydration or other causes of hypovolemia.

Comparing of models of Marsh and Schnider: The 'Marsh' model is identical to that described by Gepts et al (1987) except that the central volume of distribution (V_1) has been increased to 0.228 l/kg. The original vale for the k_{e0} was 0.26 min-1. However the data on which this was based have not been published in the peer-reviewed literature, but it is comparable with the value 0f 0.2 min-1 found by Billard et al (1997).

More recently Struys et al (2000) found that a k_{e0} value of 1.2 min-1 more accurately predicted the time course of clinical effect. This k_{e0} when used with the Marsh kinetic data results in an estimated TTPE (time to peak effect) of about 1.6 min., which is consistent with the findings of other researchers (Schnider et al, 1998). This is the combination used in the Base Primea TCI System, and as an option in the Asena PK system, and results in slower changes of the plasma concentration when the system is used in the 'effect-site targeting' mode.

The 'Schnider' model is based on a study where 24 volunteers received propofol and simultaneous kinetic and dynamic data were collected. There are 4 co-variates (total body weight, age, height and lean body mass). The k_{e0} in this system is 0.456 min-1 and the TTPE is 1.69 min (19, 20).

The performance of target-controlled infusion systems in a given population can be assessed by calculation of four criteria of predictive accuracy (Varvel et al, 1992). These are MDPE (median performance error; a measure of bias); MDAPE (median absolute performance error; a measure of accuracy); WOBBLE (a measure of the intra-individual variability in errors) and DIVERGENCE (a

measure of any trend over time in the size and magnitude of errors). Accepted standards for MDPE and MADPE are considered as 10-20% and 20-40% respectively.

KEY POINTS:

Rationale for TCI: concentration = infusion rate/ clearance.

Utility: easier to titrate drug concentration to stimulus strength than by manual dosing.

Questions: which kinetic model is the best? The present kinetic models included in the systems mentioned are based on data from small numbers of ASA1 or 2 subjects. There are still some important questions to address -

Kinetic models – data derived from different sources; some in patients, some in volunteers.

Variability of kinetics/ dynamics due to disease, ageing, intercurrent therapies

Overdose leads to cardiorespiratory side-effects; under-dosing has the potential for awareness in paralysed patients

Different kinetic models have different values for volumes of distribution and $k_{e0.}$

PK-PD: k_{e0} varies with age and disease

Effect of drug concentration on kinetics – high input drug concentrations may cause cardiovascular depression and decreased liver blood flow [and hence reduced hepatic drug clearance] (Sear et al, 1994).

The use of TCI is expected to avoid over-dosage; is easier to titrate concentration so allowing better titration of concentration to effect; and with some delivery systems taking account of a range of patient covariates. A recent Cochrane Collaboration Review has compared TCI and manually controlled infusions for general anesthesia or sedation in adult surgical patients (Leslie et al, 2008). The results from 20 RCTs and 1759 patients are not completely as expected!

Some solutions: use on online drug concentration measurement and Bayesian Modelling to adjust input rates to observed concentrations Titration of input rates to a dynamic endpoint (EEG, evoked potentials etc); Use of population modelling to define pharmacokinetic confounders more fully.

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