

*Drug
Administration
with Target
Controlled Infusion
Systems and
Future
Applications*



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Target Controlled Infusion Systems

Several drugs have favourable pharmacokinetic profiles for use in total intravenous anaesthesia (TIVA) but the use of intravenous agents for maintenance of anaesthesia requires a different technique compared with volatile anaesthetics delivered via calibrated vaporisers. Several manual infusion schemes have been proposed to maintain satisfactory anaesthesia with the aim of maintaining constant blood concentrations during anaesthesia. However, such schemes have the disadvantage of inability to vary the blood concentrations in a predictable manner to respond to changing surgical and anaesthetic requirements.

There was a need for a system which enabled the anaesthetist to alter the depth of anaesthesia in as simple a manner as that used for volatile agents and target-controlled infusion systems were developed to administer propofol and other drugs which fulfil this requirement. In the case of propofol, the pharmacokinetic parameters describing the distribution and elimination were incorporated into a target controlled infusion (TCI) system. This enabled the anaesthetist to achieve and maintain the desired blood concentration of propofol appropriate for any individual patient and level of surgical stimulation at any time in as simple a manner as that for volatile agents. The TCI system was assessed by comparing the predicted with the measured blood concentrations of propofol and by asking anaesthetists for their view of the value of the target-controlled infusion system.

One of the first TCI systems was based on a standard desktop computer which transmitted infusion rates to a computer-controlled lmed 929 infusion pump. This system proved that the technique could work well but was large and cumbersome. Replacing the desktop computer with a Psion II hand-held computer enabled a device to be produced with about the same size as a normal vaporiser. Both these systems performed satisfactorily and were used for many clinical studies. However, they were based on non-medical components.

The next development was to produce a device which was designed from the beginning as a medical-grade system to act as a flexible infusion platform. This TCI system was produced with a double microprocessor design to maximise safety. Each microprocessor calculated the drug concentration separately from different information sources and the two calculations were compared. This complete control system was miniaturised into the 'Diprifusor' module and this is now incorporated into dedicated TCI systems.

Differences between manual infusions and TCI

The essential difference between a manual infusion and a target controlled infusion is that with a manual infusion, the anaesthetist has no definite knowledge of the blood concentration and therefore of the anaesthetic effect. In contrast with a TCI, the system displays the best estimate of the blood concentration of the drug, and also allows the anaesthetists to achieve any change in the concentration as accurately and as rapidly as possible.

Twenty-seven of 30 UK anaesthetists indicated that TCI systems had increased their use of propofol for maintenance of anaesthesia. The reasons were greater ease of administration and more confidence regarding the predictability of anaesthetic effects compared with a manually controlled infusion. Data obtained from 770 patients anaesthetised with the system showed wide

variations in the target concentrations selected and also in the number of alterations of propofol concentration. This reflects the need for a flexible infusion system which can be used to titrate the level of anaesthesia for any individual patient against the level of surgical stimulation.

Open TCI Systems

Open TCI Systems have now been introduced by Alaris (*Aseba Open TCI*) and Fresenius (*Base Primea*) which allow non-tagged syringes to be used with generic, low-cost propofol. This has greatly decreased the cost associated with total intravenous anaesthesia. The Alaris system provides the same pharmacokinetic model as the Diprifusor while the Fresenius system provides different models from the standard used in the Diprifusor TCI system.

Different Pharmacokinetic Models

The pharmacokinetic model used in the Diprifusor was described by Marsh and his colleagues. It was a relatively simple 3-compartment model which adjusted the volume of the central compartment based on patient weight. Age was not used as a co-variate except for paediatric patients, but this paediatric model was not implemented in the Diprifusor system.

An alternative model has now been introduced which was described by Schnider several years ago and which uses age as a co-variate in an attempt to improve the accuracy of the model. The Schnider model has a much smaller volume of the central compartment and a much faster equilibration with the effect site. The aim of any model system is to provide a valid representation of the real system. Several studies have compared the Marsh and Schnider models during transitions from the conscious to unconscious state, and during simultaneous measurement using different types of anaesthetic depth monitors. The results demonstrate that the Schnider model does not predict well the equivalent changes which occur in several measures of anaesthetic depth.

TCI Remifentanil

Remifentanil is a rapidly acting opioid but its unique feature is the lack of any context sensitive half time. This means that the concentration will always half in 3-5 minutes independent of any pathological changes in the patient. However, if the infusion rate of remifentanil is increased, only 57% of the final concentration at the effect site is achieved after 5 minutes. If the infusion rate is halved or doubled, then a stable, steady state is not achieved even after 15 minutes. In contrast to using a manual infusion, rapid changes are obtained with TCI when increasing and decreasing the blood concentration and the system will achieve the most accurate and rapid change possible with the drug.

A further issue to consider is the pharmacokinetic variation with age and gender. If a dose of 1 µg/kg remifentanil is given to a young, tall, slim female, the peak blood concentration will be approximately 13 ng/ml. The patient would be expected to breathe at an effect site concentration of about 2 ng/ml and respiration will start at about 4 minutes after the administration of the single dose.

In contrast, the administration of the same dose to an elderly obese and short female will

achieve a peak blood concentration of about 28 ng/ml and the effect site concentration of 2 ng/ml would be achieved about 10 minutes after the dose was given. TCI remifentanyl allows the blood concentration to be targeted as accurately as possible for the individual patient and so allows the titration of dose to achieve the required clinical effect as simply as possible.

Effect-Site Control

We know that anaesthetic drugs do not exert their actions in the blood but at an *effect-site*. This is a theoretical compartment which is linked to the 3-compartment model and which explains the delay between achieving a blood concentration and the final effect of the drug. It is a theoretical compartment whose kinetics have to be deduced and not measured using some surrogate marker of the drug effect. The value obtained for the effect site kinetics will depend to some extent on the surrogate marker used.

The new *Open TCI* systems can also offer the possibility of targeting the theoretical concentration in the effect site instead of the concentration in the blood. Effect site control deliberately allows the blood concentration to overshoot the effect site target concentration but calculates the exact moment when the blood concentration should be reduced to allow the effect concentration to be achieved with no overshoot.

There are relatively few studies which have used effect site control, but there are potential advantages in terms of the speed of response in that the blood concentration can be increased to rapidly drive the drug into the effect site and so produce the required effect quickly. However, there are also potential disadvantages such as enhanced adverse cardiovascular effects, and further studies are required of this mode of TCI administration. It is well known that while there may be variations between the blood concentrations using a TCI system, the pharmacodynamic variations are much greater. This may be partially caused by marked variations in the effect site kinetics and so the use of effect-site control may not provide the degree of precision which anaesthetists may require in situations such as sedation where a narrow therapeutic range may exist between adequate sedation and anaesthesia.

Practical precautions and pitfalls

The essential point about the use of TIVA is that the drugs must be delivered into the circulation. A secure intravenous access is required of adequate size to allow the infusion pump to run at its maximum rate of 1200 ml/hour. Ideally this access should be visible at all times to ensure the infusion is not disrupted. If drug and IV fluids are connected to the same cannula by means of a T-piece or three way tap, it is necessary to ensure that the fluids are running, to prevent reflux by using a one-way valve fitted to the fluid infusion line and to minimize the use of extensions to reduce the dead-space.

Co-administration of drugs by the same giving set is not ideal as a change in the rate of one infusion can affect the other, especially if there is a significant dead-space after the common connection or T-piece. The most reliable method is to use a separate, dedicated access site.

If the new Schnider model is being used with one of the newer *Open TCI* systems, then the

anaesthetist must understand that the pharmacokinetic and dynamic model is completely different from that used in the Marsh or *Diprifusor* model. The values and times of onset of the propofol action which are displayed using the Schnider model will not be the same and may not correspond to other measures of drug action.

Closed-Loop Anaesthesia

Closed-loop anaesthesia (CLAN) systems have been developed using blood pressure or median frequency of the compressed spectral array. However, these CLAN systems have only been used in paralysed patients during surgery and required intervention often because of unsatisfactory conditions.

Systems based on the bispectral index have been reported to have successfully controlled the level of sedation and anaesthesia in patients during elective surgery. A closed-loop control system based on the AEPex has been used to control the intravenous administration of propofol in 100 patients breathing spontaneously and also in those who received paralyzing drugs during surgery. The quality of anaesthesia was judged to be satisfactory as assessed by scores of autonomic activity, cardiovascular stability and minimal movement during surgery. Patients were visited postoperatively and there was no occurrence of awareness during the surgical procedures in any patient.

An automatic system to deliver anaesthesia can therefore be produced relatively easily. However, the regulatory difficulties are very large and it is unlikely that such systems will be available widely in the near future.

Patient-Controlled Sedation

Sedation allows patients to undergo procedures which they would otherwise be unable to tolerate. The sedation must not contribute any morbidity or mortality to the procedure and ideally should be safe when used by surgeons and physicians as well as anaesthetists. The technique used must allow for rapid alterations in the level of sedation. It should allow the patients to recover rapidly full consciousness without rebound or emergence effects at the end of the procedure to ensure that they are in a safe condition for discharge from the recovery area.

Patient-controlled analgesia is a well-recognised technique for pain control and patient-controlled sedation (PCS) has been described for sedation. The patient uses a device similar to a PCA system to self-administer single doses of a sedative. Most studies comparing PCS with propofol or midazolam, have reported that propofol produced a more rapid onset of sedation with faster return to normal following the procedure.

Patient-maintained sedation (PMS) allows the patient to control the target concentration of propofol using a button push. A study of this technique during surgery under LA suggests that it provides rapid, safe and effective relief of anxiety. Safety and efficacy of the PMS system has been assessed and has shown to be very acceptable to both patients and surgical staff. While the use of a PMS system targeting blood concentration has been shown to be safe and effective in clinical use, there are potential problems with the time to achieve a satisfactory level of sedation and the possibility of overshoot. The latest development under evaluation, which is aimed to solve these problems, is a PMS system targeting the effect site concentration.

With more procedures being undertaken using minimally invasive surgical techniques, there will be increased requirements for conscious sedation. The techniques we employ must be safe and efficacious and may be directed towards allowing the patient to participate more in the drug delivery. PMS propofol may fulfil this requirement and the eventual aim is to provide a TCI system which can be used without the direct supervision of an anaesthetist.

Conclusions

General anaesthesia is a dynamic balance between the level of hypnotic, analgesic and the effects of stimulation from surgery or instrumentation. Patient requirements for both hypnotics and analgesics vary considerably within and between patients. The ability to titrate is therefore an essential feature of any anaesthetic technique, and the simpler the technique makes for titration of the patient, the easier it will be to use in the busy environment of an operating theatre.

The aim of using a TCI system is to reach as rapidly as possible a steady concentration of drug against which the anaesthetist can assess the adequacy of hypnosis and analgesia. The latest TCI systems have both extended the range of drugs available to infuse with this technique and decreased the overall cost.

New developments may extend the use of TCI systems into patient-controlled sedation with resulting improvement in patient safety. Closed-loop control of anaesthesia is technically possible but regulatory difficulties must be overcome before such systems become standard in the anaesthetic workplace.