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Hands Free Anesthesia: Target Controlled Infusion Systems

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1. Introduction

The target of every form of drug delivery is achieving and maintaining a therapeutic time course of drug effect, while avoiding adverse effects. Intravenous (IV) drugs are usually given using standard dosing guidelines either as a bolus dose or by continuous infusion. Bolus doses are typically administered with a handheld syringe and infusions with an infusion pump. The only patient covariate that is incorporated into a dose calculation is the body weight, while other parameters like age, sex, creatinine clearance etc are often ignored because of the complex mathematical relationship of these covariates while dosing. Target-controlled infusion (TCI) is a technique of infusing IV drugs to achieve a user-defined, predicted ("target") drug concentration in a specific body compartment or tissue of interest. TCI systems can rapidly titrate response as necessary, can easily alter depth of anaesthesia and also maintain steady concentrations when required. The potential benefit to clinicians is the more precise titration of anesthetic drug effect. TCI systems can also be instructed to overshoot the desired concentration in the plasma to accelerate the rate of onset of drug effect. (1,2)

When using pharmacokinetic-derived models specific to a particular drug, a TCI system incorporates patient characteristics (weight, height, age, sex, and additional biomarkers) to achieve a targeted serum-level concentration, while allowing the clinician to make changes based on clinical or physiological (bispectral index monitoring) indicators. (3)

Target controlled infusion (TCI) system are now in use as a standardised infusion system and also as a part of routine anaesthesia technique

2. History

In 1919, Widmark described the kinetics for accumulating drug amount in the body during constant rate infusion using constant rate and first-order elimination in a drug adopting single compartmental kinetics.

In 1968, Kruger-Thiemer published a mathematical approach for calculating infusion rates to reach and maintain a steady-state blood concentration of a drug applied to 2 or more compartments. Their pharmacokinetic models could be used to design efficient dose regimens applying Bolus, Elimination, Transfer (BET) regimen consisting of a bolus dose calculated to fill the central (blood) compartment, a constant-rate infusion equal to the elimination rate, and an infusion that compensates for transfer to the peripheral tissues: [exponentially decreasing rate]

Vaughan and Tucker applied this model to a lidocaine infusion. Schüttler and Helmut Schwilden performed the first TCI administration in Bonn, Germany, on May 1, 1979.

In 1981, Schwilden published a generalized method for calculating the dosage schemes in linear kinetics. Two years later, Schüttler, Schwilden, and Stoeckel published their first clinical experience with the CATIA system, the first practical TCI system involving a plasma-targeted TCI of etomidate (0.3 µg/mL) and alfentanil (0.45 µg/mL) to induce and maintain anesthesia.

In 1986, Jerry Re developed the computer assisted continuous infusion (CACI)at Alabama University to titrate fentanyl and sufentanil during cardiac surgery. This approach allowed approximate adjustment of the targeted plasma concentrations during infusion, which was not possible with the BET approach.

In 1988, at Leiden, the Netherlands, Ausems and Hug used a developed TIAC to evaluate the accuracy of their alfentanil model during plasma-controlled TCI. They documented intersubject variability between measured and predicted concentrations between 22% and 32%, which is typical of alfentanil PKs, and concluded that TCI can be used to rapidly attain a relatively stable plasma concentration and to facilitate titration to the requirements of an individual patient during anesthesia. They found that repeated bolus injections resulted in rapid fluctuations in alfentanil concentrations, which were not seen with TCI administration. Although both methods controlled the patients' responses to noxious stimuli, the TCI group had greater hemodynamic stability and lower incidence of side effects.

In Bristol, United Kingdom, Tackley et al. developed a propofol TCI system using the Bolus-Elimination-Transfer (BET) approach based on the previously derived PKs from a propofol single-bolus study. They found that blood concentrations were close to the predicted target. A decade later, they incorporated ketamine into the device.

In 1988 to 1990, Shafer and his colleagues developed the STANPUMP (for STANford PUMP), written in C language. This supported multiple infusion pumps using an analytical solution to the 3-compartmental model to control plasma concentrations using TCI. After 1993, the authors included the algorithms to rapidly achieve and maintain stable drug concentrations at the effect-site level allowing compartment-controlled TCI. Effect-site control was a major step in providing precise titration of anesthetic drug effect.

Frank Engbers at Leiden University developed a portable system that could administer 2 drugs in TCI mode for use to study drug interactions and also an upgraded system for a TCI-patient-controlled-analgesia of alfentanil for post-operative pain with a safety loop back function using a respiration monitor.

At Glasgow University, White and Kenny developed an Atari-controlled propofol computer pump to deliver a specific targeted plasma concentration of propofol. Roberts et al at Bristol suggested that 3 μg/mL was the right plasma concentration for propofol. They developed a prototype for the Diprifusor™ module (AstraZeneca, London, UK), the first commercial TCI device. The Diprifusor module used 2 processors to solve the PK equations and ensured a double check on the infused volume to guarantee safety. Because this was to be the first commercial implementation of a microprocessor infusion device incorporating a second independent checking processor ensured safety.

In the early 1990s, Johan Coetzee and Ralph Pina from Stellenbosch University, South Africa, developed STELPUMP, controlling 2 syringe pumps simultaneously with a graphic interface.. De Smet and Struys developed a modular computer-based TCI software called RUGLOOP, written in C++ for Windows. RUGLOOP II was able to control multiple-syringe pumps simultaneously administering multiple drugs, targeting either the plasma or effect-site concentration using the bispectral index as a controlled variable. It also permitted TCI-patient-controlled analgesia and TCI-patient-controlled sedation. A simplified algorithm, developed by Shafer and Gregg to include the effect site, became the basis of all TCI systems.

Schüttler and Schwilden developed IVFEED allowing both plasma and effect-site TCI for multiple drugs. In 1999, researchers at the Facultad de Medicina Universidad de Chili developed AnestFusor using control plasma and effect-site concentrations during TCI incorporating TOOLBOX , a Windows program that can capture information from physiologic monitors and perform closed-loop controls based on feedback from the monitors.(4)

3. Principle

TCI represents an innovative method to deliver IV drugs via computer models, with goals of achieving a defined ("target") drug concentration within a specific body compartment or organ (brain). Every anesthetic agent accumulates in the tissue during drug delivery. This accumulation confounds the relationship between the infusion rate set by the provider and the drug concentration in the patient. Because tissue drug concentrations cannot be measured in real time for IV anesthetic drugs, the microprocessor uses a PK–pharmaco dynamic (PD) model to estimate plasma concentrations. The clinician enters a desired target concentration and the computer calculates the amount of drug delivered, as boluses and infusions, to achieve the target concentration and then directs an infusion pump to deliver the same. The computer constantly calculates drug concentration levels in tissues and the amount of drug required to achieve the target concentration by using a model of the PKs of the drug selected and the patient covariates. In this way, the computer's prediction of the current drug concentration serves as continuous input to the computer's pump control algorithm. (Fig 1)

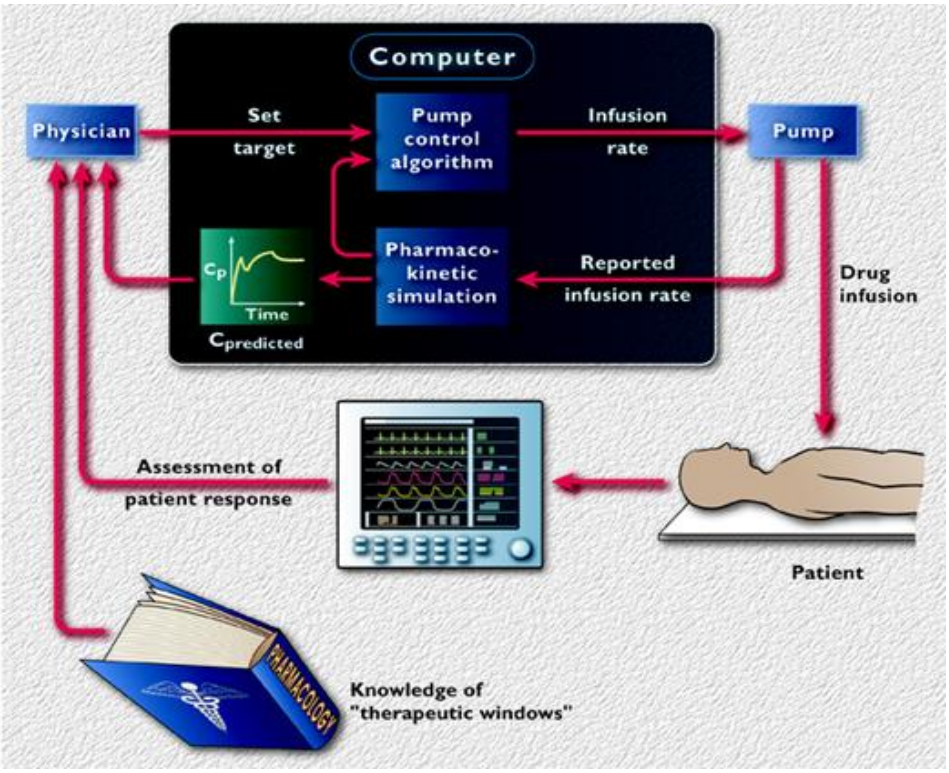

Figure 1: Components of the TCI system

The peak clinical effect of a given plasma concentration of the drug is achieved a few minutes after a bolus injection due to delay in equilibration of the plasma concentration (Cp) with the effector site. The rate of this equilibration

between plasma and effector site concentration (Ce) is described by the keo, which defines the proportional change of concentration gradient between plasma and effect site in unit time. This delayed response depends on the lipid solubility, degree of ionisation of the drug as well as cardiac output and cerebral blood flow. Incorporation of the effect-site equilibration delay constant, keo, in the complex PK equations not only explains this delay in peak action of a drug but also helps to predict its concentration at the effect site at any given point of time of TCI infusion.. While higher keo values indicate quicker transfer or equilibration, lower values indicate slower or delayed equilibration with the effect site. The TCI systems which target Ce lead to the achievement of higher initial Cp for quickly achieving the target Ce. This temporary overshoot of the plasma concentration depends on the keo (smaller overshoot for larger keo and vice versa).

An advantage of using TCI devices is that the anesthesiologist can track effect site concentration both during onset of anesthesia (Ce LOC) as well as recovery (Ce REC). Theoretically, the real effect site concentration of a hypnotic drug should be similar at loss and recovery of consciousness in the same patient. The time to reach this Ce after switching off anesthetic can be predicted by the TCI device and this can aid the anesthesiologist in planning termination of the anesthetic drug infusion prior to the conclusion of surgery and thereby save operating room time and predict recovery from anesthesia.

Besides clinical application in anesthesia, target controlled systems will play a significant role as research tools in the evaluation of drug interactions in anesthesia and in the development of new control techniques for the administration of sedative and analgesic drugs in the peri operative period.

Several physiological factors influence the pharmacokinetics of drugs at extremes of age. In elderly there is a smaller central volume of distribution, decreased clearance, increased receptor sensitivity to drugs and increased time to peak effect. The elderly lose consciousness at lower blood concentrations of anesthetic drugs and also develop cardio-respiratory compromise at increased concentrations. In the elderly and frail it is best when inducing anesthesia with TCI propofol, to start at a very low target concentration and increase the target concentration in small steps every few minutes.

TCi in children is not very popular. Children tend to have a large central compartment volume and rapid clearance of IV drugs. Therefore they require relatively higher dose of intravenous (IV) agent per-unit of body weight and higher maintenance infusions rates than the weight corrected dose for adults. There is a significant overestimation in blood concentrations leading to metabolic acidosis, lipaemia and fatty liver infiltration with use of prolonged propofol infusion in intensive care. The Paedfusor model performs better in children than the Marsh model.

Types of TCI

The TCI systems are identified as open- and closed-loop systems.

a) In the open-loop systems, the providers select a specific drug and a specific pharmacokinetic or pharmacodynamic model from the drug library incorporated in the device. Published models are embedded in the pumps for propofol, remifentanil, sufentanil, and alfentanil. A limitation of this delivery technique is that it there is no feedback from the patient necessitating continuous clinical assessment of the patient and refining of the target.(5)
b) A closed-loop system is a system wherein the measured output(s) is used by a controller to determine a new input to the system. The computer controller evaluates a real-time measure of drug effect such as a peripheral nerve stimulator for muscle relaxants or the processed electroencephalogram for hypnotics, and adjusts drug delivery on the basis of that measure (*i.e.* the feedback signal comes from a monitor). The controller which closes the loop can be manual or automated. A single closed-loop controller in anesthesia has been used for hypnosis, neuromuscular blockade, analgesia, arterial blood pressure control, and fluid optimization. There are three elements in every closed-loop system:
   - A central operating software (brain of the system)
   - One or more target-control variables (e.g. hypnosis monitor)
   - One or more drug delivery systems (infusion pump).

In comparison to the open-loop system, the closed-loop system may offer the advantages of more precise dosing, decrease in some workload functions, improved and standardized control of the depth of sedation and anesthesia, decreased consumption of drug, improved hemodynamic stability, faster postoperative recovery, and minimized individual operator variability in titration of the sedative agent.(6)

Available TCI Models

- Marsh model used by Diprufusor for propofol FOR AGES>16 years
- Schüttler and White-Kenny (WK) models for propofol
- Schnider model for propofol ideal for elderly population
- Kataria and Paedfusor model in children
- Minto model for remifentanil

Commonly available pumps include: Fresenius vial master TCI [diprufusor], Alaris IVAC TCI, Terumo TE372 TCI (Diprufusor), Alaris Asena PK and Fresenius Base Primea. (Fig 2) Checklist as per Table 1 is advisable.

Table 1: Checklist for setting up TCI systems

1) Use only dedicated pharmacokinetic TCI pumps
2) Ensure that you are trained in use of the chosen pump and pharmacokinetic model
3) Ensure the pumps have been serviced in the past 12 months
4) Ensure the pumps are plugged into the mains
5) Ensure the batteries are charged
6) Ensure that the drug dilutions are correct and are entered correctly into the pump
7) Ensure that the correct syringe type and size data are entered and that the syringes are mounted correctly
8) Ensure that the pump is programmed for the drug actually attached to it

9) Ensure that the low and high infusion pressure alarms are set (to warn of disconnection and a 'tissued' or displaced cannula, respectively)
10) Ensure that the correct patient data are entered
11) Consider if the targets set are appropriate to the patient's age and ASA status
12) What is plan B if the pump(s) fail?

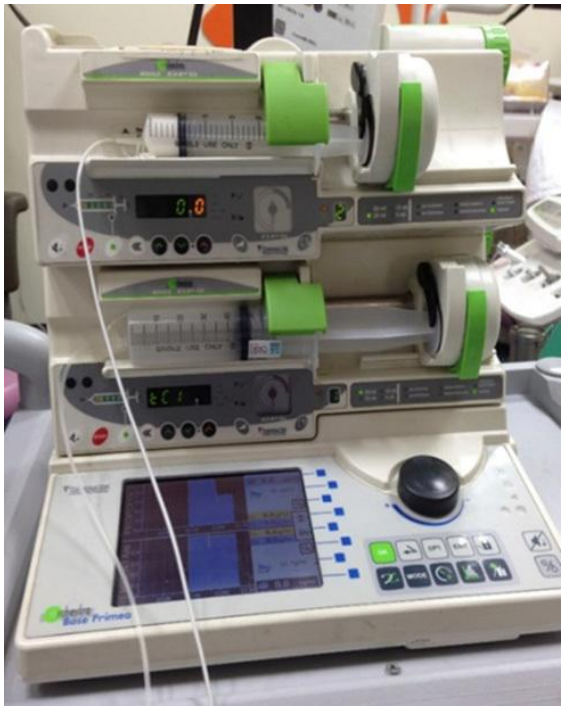

Figure 2: Target controlled infusion pumps are used to administer propofol and remifentanil.

4. The Future of TCI

Future perspectives of TCI are related to model selection and optimization, incorporation of more drugs, connectivity issues with drug advisory displays and anesthesia information management systems, integration into closed-loop systems, and as a tool to incorporate best practices into perioperative medicine.

Model optimization using more generally applicable models might be useful when anesthetizing different populations, such as obese patients, children, and neonates. Because the various TCI pump manufacturers developed their products independently from each other using different advisory boards and literature searches, the availability of different models for the same IV drugs in products from different manufacturers has the potential to create confusion for clinicians unfamiliar with the pharmacologic principles governing TCI. This experience has limited the expansion of the technique despite its clinical benefits.

Most commercially available open TCI systems include models for propofol, fentanyl, sufentanil, alfentanil, and remifentanil. Because clinicians are asking for additional drugs (e.g., dexmedetomidine, ketamine, and benzodiazepines), better interaction among the pharmaceutical companies, device manufacturers, device and medicines regulatory agencies must provide consistent standards for the PK models for the same drug.

Connectivity of medical equipment remains a significant problem in anesthesia. Standardized real-time reporting from TCI devices to anesthesia information management systems provides the ability to capture dose and predicted concentration. These data can be then used to expand the automated safety shell that supplements anesthesiologist vigilance with computerized vigilance, adding to the safety potential of TCI anesthetic drug delivery systems.

TCI knowledge is explicitly mentioned as core competencies or knowledge in the syllabi for basic and intermediate training of anesthesiologists: Specific topics included in the examination are:

- Types of models available (1-, 2-, and 3-compartment models), PK parameters: volume of distribution, half-life and time constant, clearance.
- Context-sensitive half-time: comparison of drugs, e.g., propofol, fentanyl, and remifentanil.
- Setting up TCI system to deliver both induction and maintenance levels of IV agents.
- Effects of renal and/or hepatic impairment on drug disposition and elimination of influence of renal replacement therapies of commonly used drugs.

5. Conclusions

TCI is an advanced method of TIVA using a special infusion pump which is incorporated with software, consisted of an algorithm that based on pharmacokinetics (PK) profile of the specific drugs and age appropriate parameters. The availability of anesthetic and analgesic drugs suitable for use by continuous infusion and advances in computer technology have helped improve the popularity of the use of TCI for anesthetic agent administration, whether for induction or maintenance of anesthesia or simply for sedation or analgesia. TCI is also used to provide stable serum concentrations of hypnotics/narcotic analgesics to facilitate studies of monitors of anesthetic depth or simply to provide stable anesthesia.

TCI is used to provide sedation or anesthesia for patients undergoing a wide range of types of diagnostic and therapeutic procedures and currently limited to the pediatric population. Possible reasons include lack of knowledge of, or exposure to, the technique in children, concerns about the validity of the models in children, and fears that enabling the use of pumps programmed with both adult and pediatric models may compromise safety. (7,8)
TCI systems can only be as good as the pharmacokinetic model with which they are programmed. Although the plasma has been the target site for most early TCI applications, the effect site is the more logical target. for an adequate method to define and describe appropriate IV anesthetic concentration targets (*i.e.* , a "MAC" equivalent for IV drugs). Intravenous anesthetic pharmacodynamics have traditionally been characterized in terms of a CP^{50}, the steady-state plasma concentration required to produce a 50% probability of some specified effect. However, it is somewhat difficult to apply this information to the selection of an appropriate TCI target, because the methods used to identify these CP^{50}s have not been fully standardized as with MAC (some CP^{50}s relate to loss of consciousness, others to

movement and hemodynamics; some are estimated in the presence of other drugs, etc.).

TCI is a useful tool that helps facilitate smooth and accurate provision of "hands-free" anesthesia and growing in popularity among anesthesiologists and now an integral part of several new and exciting developments, such as computer-controlled anesthesia, and patient-maintained sedation and analgesia..

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