The History of Target-Controlled Infusion

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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. In this review, we describe the pharmacokinetic principles of TCI, the development of TCI systems, and technical and regulatory issues addressed in prototype development. We also describe the launch of the current clinically available systems. (Anesth Analg 2015;XXX:00–00)

The goal of every form of drug delivery is achieving and maintaining a therapeutic time course of drug effect, while avoiding adverse effects. IV drugs are usually given using standard dosing guidelines. Typically the only patient covariate that is incorporated into a dose is a metric of patient size, typically weight for IV anesthetics. Patient characteristics such as age, sex, or creatinine clearance are often not included because of the complex mathematical relationship of these covariates to dose. Historically there have been 2 methods of administering IV drugs during anesthesia: bolus dose and continuous infusion. Bolus doses are typically administered with a handheld syringe. Infusions are typically administered with an infusion pump.

Every anesthetic drug accumulates in tissue during drug delivery. This accumulation confounds the relationship between the infusion rate set by the clinician and the drug concentration in the patient. A propofol infusion rate of 100 μg/kg/min is associated with a nearly awake patient 3 minutes into the infusion and a highly sedated or asleep patient 2 hours later. By using well-understood pharmacokinetic (PK) principles, computers can calculate how much drug has accumulated in tissues during infusions and can adjust the infusion rate to maintain a stable concentration in the plasma or the tissue of interest, typically the brain. The computer is able to use the best model from the literature, because the mathematical complexity of incorporating patient characteristics (weight, height, age, sex, and additional biomarkers) are trivial calculations for the computer.[1,2] This is the basis of a third type of anesthetic drug delivery, target-controlled infusions (TCI). With TCI systems, the clinician enters a desired target concentration. The computer calculates the amount of drug, delivered as boluses and infusions, required to achieve the target concentration and directs an infusion pump to deliver the calculated bolus or infusion. The computer constantly calculates how much drug is in the tissue and exactly how that influences 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.

During surgery, the level of surgical stimulation can change very quickly, requiring precise, rapid titration of drug effect. Conventional infusions cannot increase drug concentrations rapidly enough to account for abrupt increases in stimulation or decrease concentrations rapidly enough to account for periods of low stimulation. Conventional infusions cannot even maintain steady drug concentrations in the plasma or brain during periods of constant stimulation. By incorporating PK models, TCI systems can rapidly titrate response as necessary and similarly maintain steady concentrations when appropriate. The potential benefit to clinicians is the more precise titration of anesthetic drug effect.[3]

In this review, we describe the PK principles of TCI, the development of TCI systems, and technical and regulatory issues addressed in prototype development. Two accompanying review articles cover the global use and safety issues related to this technology.[4,5]

As TCI systems evolved, investigators chose idiosyncratic terms for the methodology. TCI systems have been referred to as computer-assisted total IV anesthesia (CATIA),[6] titration of IV agents by computer (TIAC),[7] computer-assisted continuous infusion (CACI),[8] and computer-controlled infusion pump.[9] Following a suggestion by Iain Glen, White and Kenny used the term TCI in their publications after 1992. A consensus was reached in 1997 among the active investigators that the term TCI be adopted as the generic description of the technology.[10]

PHARMACOLOGIC PRINCIPLES GOVERNING TCI

In anesthesia practice, bolus doses are typically administered in units of milligrams or micrograms. If doses are adjusted for weight, then the dose will be milligrams per kilogram or micrograms per kilogram. Infusion rates are similarly set in units of milligrams per minute or micrograms per minute. If the infusion is weight based, then the rate will be milligrams per kilogram per minute or micrograms per kilogram per minute.

TCI systems use a different approach. Rather than setting the drug administration rate, the user sets a target concentration to achieve a user-defined predicted drug concentration in a specific body compartment or tissue of

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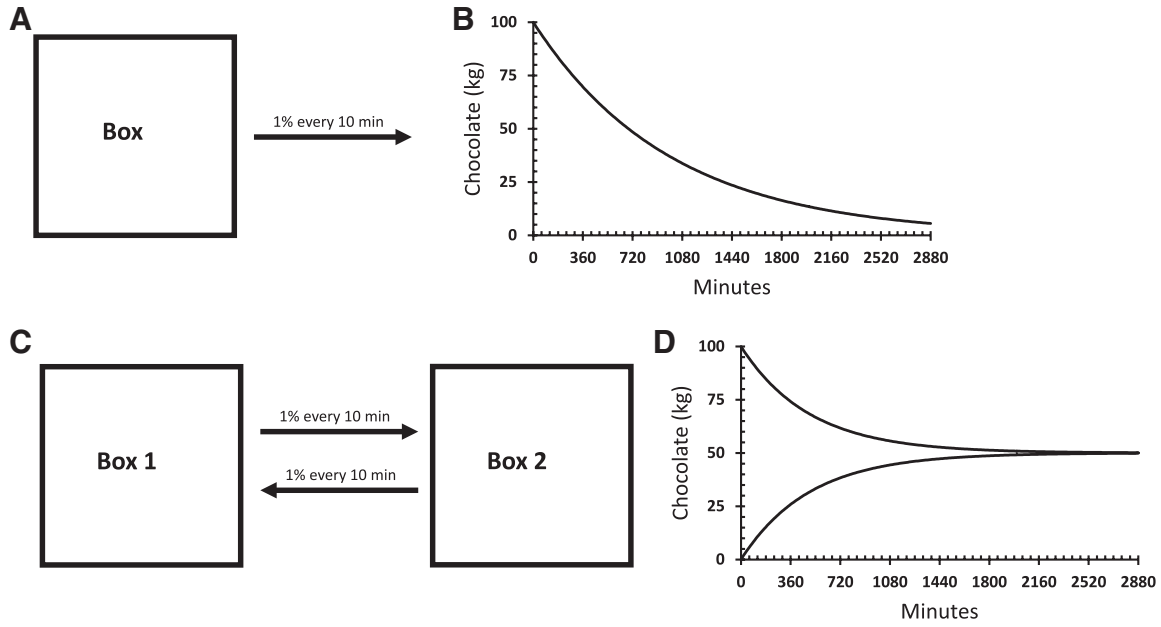

Figure 1. The chocolate model. A, A box full with 100 kg of chocolate where you remove 1% of the chocolate every 10 minutes. B, The decline of the chocolate in the box shown in (A). C, A scenario where you start with a full box 1 and an empty box 2. You transfer 1% of the chocolate every 10 minutes from box 1 in box 2 and you return the same amount every 10 minutes from box 2 to box 1, finally creating a steady-state situation in which a same amount is transferred per time between both boxes. D, The changes in chocolate amount in both boxes in time.

interest. Anesthesiologists find this intuitive, because it is exactly how we administer inhaled anesthetics. The analogy to dosing inhaled anesthetics is strong. We often think of end-tidal inhaled anesthetics, but we realize that the target organ is the brain. End-tidal concentrations are only interesting because the brain gradually equilibrates to the end-tidal concentration. Similarly, TCI systems model the plasma drug concentration. However, that is only interesting because the brain gradually equilibrates with the plasma. Anesthesiologists may initially administer inhaled anesthetics to achieve a higher end-tidal concentration than desired, by using the overpressure to accelerate the onset of drug effect in the brain. As will be described, contemporary TCI systems can be instructed to overshoot the desired concentration in the plasma to accelerate the rate of onset of drug effect. It turns out that this approach matches what we do clinically when we first administer a bolus followed by a continuous infusion.[11]

The fundamental characteristic of TCI systems is incorporating tissue drug concentrations into the calculations of the infusion rate required to achieve the target concentration. Because tissue drug concentrations cannot be measured in real time for IV anesthetic drugs, the computer uses a PK–pharmacodynamic (PD) model to estimate the concentrations. With this information, the computer calculates the infusion rate required to reach and maintain a specific predicted plasma or effect-site concentration.

Thus, an anesthesiologist using a TCI system to administer an IV agent is able to set and change a target concentration, basing the choice of target concentration on observation of clinical effect. Multicompartment PK–PD models are used by TCI systems to calculate the infusion rates required to reach and maintain the target concentration. A computer or microprocessor is required to perform the calculations and control the infusion pump.

TCI systems target a concentration in the plasma or at the site of drug effect. The basic mathematics is surprisingly trivial. Let's say that you have a box full with 100 kg of chocolate. Every 10 minutes, you remove 1% of the chocolate from the box. Figure 1A depicts this setting. After 10 minutes, there would be 99 kg of chocolate in the box. Ten minutes later, there would be 98.01 kg ($99 - 99 \times 0.01$). Ten minutes later, there would be 97.03 kg ($98.01 - 98.01 \times 0.01$). Repeating this process (e.g., with a spreadsheet): after 4 hours, there would be 78.5 kg; after 1 day, there would be 23.5 kg; after 2 days, there would be 5.5 kg; and after a week, just 0.004 kg. The decline in chocolate over time is shown in Figure 1B.

Let's consider a slightly different scenario. Rather than eating the chocolate, you put it in another box. As the first box loses chocolate, the second box gains chocolate. Nearly all of the chocolate will eventually be in the second box. However, what happens if you apply this same rule to the second box, returning the chocolate to the first box? The scenario is shown in Figure 1C. What happens is that as the chocolate increases in the second box, some of it starts returning to the first box, because the process is symmetrical. Eventually you reach steady state, where each box has 50 kg of chocolate. This is shown in Figure 1D. Things are still happening at steady state. Specifically, every 10 minutes you still transfer 0.5 kg of chocolate (1%) from box 1 to box 2. However, because it is symmetrical, you also transfer 0.5 kg of chocolate from box 2 to box 1, so there is no net change in either box.

We can reduce this to an equation by simply saying what the transfer rule is for each box. The equation will take the form: chocolate coming into the box minus chocolate leaving the box:

$$\text{Change in chocolate in box 1} = \text{Chocolate in box 2} \times 0.01 - \text{Chocolate in box 1} \times 0.01$$

Change in chocolate box 2 =

Chocolate in box 1 × 0.01 – Chocolate in box 2 × 0.01

We will replace "change in" by the mathematical symbol Δ. We will replace chocolate in box 1 by "C_1" and chocolate in box 2 by "C_2," and we will obtain the following equations:

$$\Delta C_1 = C_2 \times 0.01 - C_1 \times 0.01$$

$$\Delta C_2 = C_1 \times 0.01 - C_2 \times 0.01$$

Let's now label the rate of transfer from box 1 to box 2 as K_{12}, and the rate of transfer from box 2 to box 1 as K_{21}. The chocolate transferring equation can be reduced to:

$$\Delta C_1 = C_2 K_{21} - C_1 K_{12}$$

$$\Delta C_2 = C_1 K_{12} - C_2 K_{21}$$

These are called difference equations. They are a simplified manner of representing differential equations. Figure 2 shows the PK model that is used for nearly all IV drugs, including the time delay between the plasma and the site of drug effect (e.g., the brain).[12,13] Because there are more boxes, the PK model requires more housekeeping than the chocolate model. Other than the requirement for more housekeeping, the model is exactly the same. Let's call the amount of drug in compartments 1, 2, 3, and the effect site as A_1, A_2, A_3, and A_e, respectively. The difference equations are as follows:

$$\Delta A_1 = A_2 K_{21} + A_3 K_{31} - A_1 K_{10} - A_1 K_{12} - A_1 K_{13} + \text{Drug input}$$

$$\Delta A_2 = A_1 K_{12} - A_2 K_{21}$$

$$\Delta A_3 = A_3 K_{13} - A_3 K_{31}$$

$$DA_e = A_1 K_{1e} - A_e K_{e0}$$

This is all the computer needs to do to track the concentrations of drug in all 4 compartments. It is literally trivial. The difference equations are simplified versions of the differential equations:

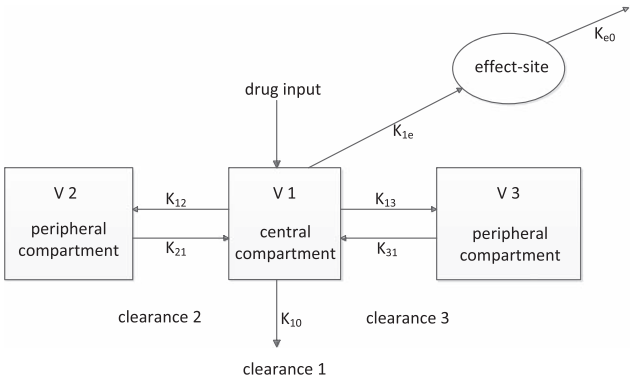

Figure 2. The 3-compartmental model, with 3 volumes of distribution (V_1, V_2, and V_3) and various k values representing the rate and direction of movement of the drug among the compartments (k_{12}, k_{21}, k_{13}, and k_{31}) or toward the outside (k_{10}). Drug is administered into a central compartment, from which it is eliminated. Drug is rapidly and slowly distributed in a second and a third compartment, respectively. The 3-compartmental model is enlarged with a pharmacodynamic effect-site compartment, governing the time delay between the plasma concentration and the clinical drug effect (represented by k_{e0}).

$$dA_1(t)/dt = I(t) + k_{21}\cdot A_2(t) + k_{31}\cdot A_3(t) + k_{e0}\cdot A_4(t) - (k_{10} + k_{12} + k_{13} + k_{1e})\cdot A_1(t)s$$

$$dA_2(t)/dt = k_{12}\cdot A_1(t) - k_{21}\cdot A_2(t)$$

$$dA_3(t)/dt = k_{13}\cdot A_1(t) - k_{31}\cdot A_3(t)$$

$$dA_e(t)/dt = k_{1e}\cdot A_1(t) - k_{e0}\cdot A_e(t)$$

The difference equations describe the rate of transfer over a small slice of time, whereas the differential equations describe the instantaneous rate of transfer at time t. As a technical detail, in the differential equations, the units of k are 1/time. This is because Δ time appears in the equation (dt). Time cancels out when k is multiplied by dt. When the value of k in the differential equations is multiplied by the time slice (e.g., 10 minutes), the result is the value of K in difference equation, which is a unitless fraction (e.g., 1%). For human PKs, difference equations using a time interval of 1 second almost perfectly match the exact closed-form implementations of the differential equations.[14] Even the most basic microprocessor can manage 4 calculations per second. This approach to solving differential equations by reducing them to simple difference equations is called the Euler method, named after the Swiss mathematician who proposed it 300 years ago.[a]

Historically, multiple representations of multiple compartmental PK models have been proposed. These are simply different representations of the model shown in Figure 1. Engineers view these models as linear systems.[15] This means that when you double the dose, you double the concentrations over time. Figure 3A shows the same model as a sum of exponentials. Figure 3B shows an hydraulic model composed of tanks (volumes of distribution) connected by pipes (clearances). The tank marked "V1" is the plasma compartment. The tanks and pipes are mathematical transformations of the model in Figure 2.[16,17] PK compartment models have been developed for nearly all IV drugs in anesthesia.[9,18–27]

The classical PK model for anesthetic drugs is a 2- or 3- compartment model. The models account for the delay between the plasma concentration and the drug effect by adding an effect-site compartment (Fig. 2).[12,28] The delay in equilibration between the plasma and the effect compartment concentrations is mathematically described by a single parameter, defined as k_{e0}, the effect-site equilibration rate constant.[29] The value of k_{e0} can be determined from complex PK/PD studies combining blood concentrations with frequent measurements of drug effect.[30] It is also possible to calculate k_{e0} from the directly observed time to peak effect after a bolus injection.[17,31,32]

MANAGING THE INFUSION SCHEMES DURING TCI

The first practical TCI implementation used the bolus elimination transfer (BET) approach. First, a bolus of drug is given, calculated as the target plasma concentration times the initial distribution volume. This bolus theoretically instantly produces the target plasma concentration. Second, a maintenance infusion equal to the elimination rate is given. The maintenance infusion rate is simply the target plasma concentration times the systemic clearance. Were it not for

[a]https://en.wikipedia.org/wiki/Leonhard_Euler. Accessed July 15, 2015.

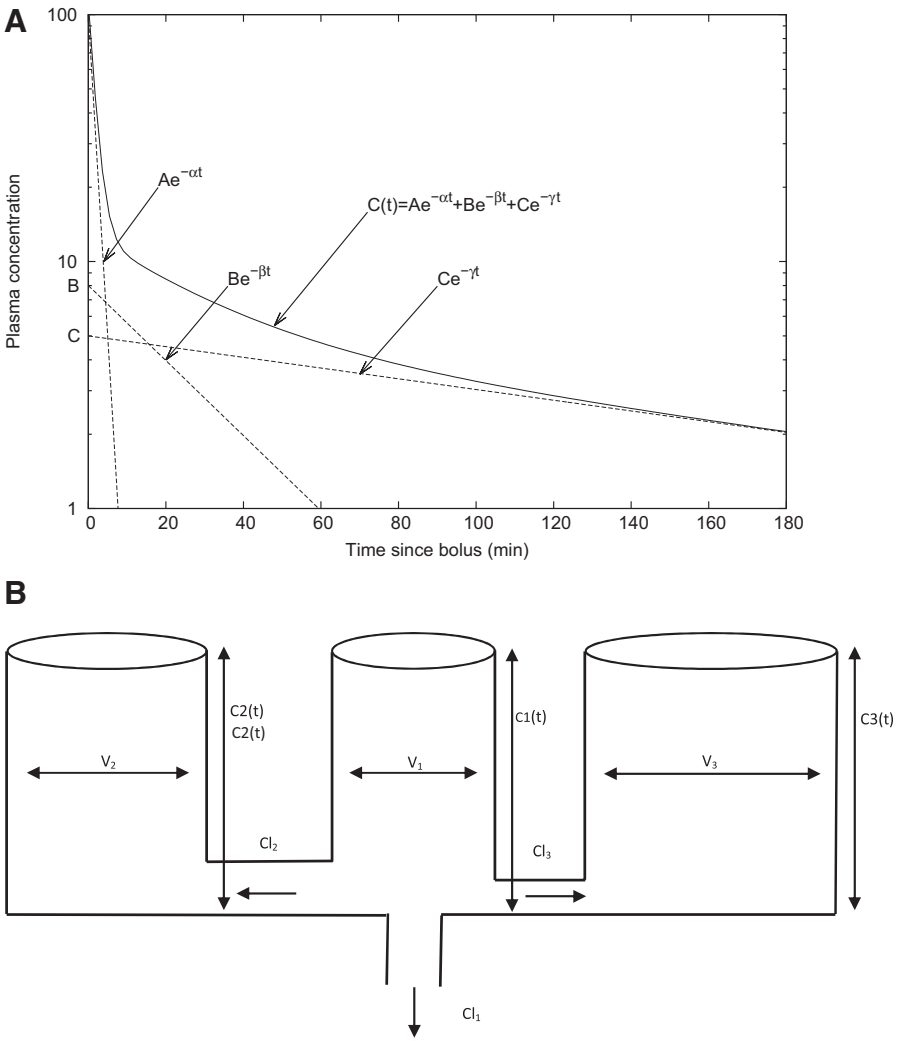

Figure 3. A, The log-linear represented time course of the plasma concentration over time observed after a bolus of an IV-administered drug. Each component term represents a portion of the curve. The individual lines associated with each component term are also shown. The triexponential curve represents the algebraic sum of the individual exponential functions. The intercepts of the curve peel are shown as A, B, and C. These are present as coefficients of the triexponential equation. B, The 3-compartmental model represented as a hydraulic model. The width of each tube is proportional to its specific volume of distribution (V_1, V_2, and V_3) and the height is proportional to the concentration. The magnitude of the metabolic (Cl_1) and intercompartmental clearance (Cl_2 and Cl_3) is depicted by the width of the tubes.

drug accumulation into the peripheral compartments, this simple bolus and infusion approach would maintain a constant drug concentration. Unfortunately, it does not work for any IV drugs used by anesthesiologists, because all our drugs accumulate over time in peripheral tissues.

A third infusion is required to replace drug transferred from the plasma to peripheral compartments. As the compartments come into equilibrium with the central (plasma) compartment, the amount of drug transferred to peripheral tissues declines exponentially. As a result, this third transfer infusion decreases exponentially, reaching 0 when the compartments are all in equilibrium (i.e., at the same concentration).[7] The infusion rate is the desired concentration × $K_{12}e^{-K_{22}t} + K_{13}e^{-K_{31}t}$. Because it is relatively straightforward to calculate using a spreadsheet, the BET scheme is still being used to develop dosing guidelines. However, the BET infusion scheme has 2 major drawbacks. First, it can only be used to target the plasma concentration. Researchers recognized that targeting the effect site would result in a better infusion strategy that more closely matches the desired time course of drug effect,[11] but this required an extension of this PK model. Second, the BET scheme is only applicable in the absence of drug previously administered. The BET scheme cannot be used if the intent is to titrate the drug-to-drug effect. This limitation led investigators to replace BET with a more flexible approach to TCI administration.[2,33]

As reviewed later, in the mid-1980s and early 1990s, various research groups developed algorithms to titrate plasma or effect-site concentrations.[14,34,35] A closed-form mathematical solution for TCI was published and implemented by Shafer and Gregg,[11] Shafer et al.,[34] and Jacobs.[8] These approaches precisely tracked drug concentration, but the infusion rate was an approximate solution. Jacobs[36] first described the exactly correct solution in 1990. The following year, Bailey and Shafer[37] published a simplified algorithm that provided exact solutions. This algorithm, extended by Shafer and Gregg[11] to include the effect site, became the basis of all TCI systems.

TCI SOFTWARE PLATFORMS

Historical Prototypes

In 1919, Widmark[38] described the kinetics for accumulating drug amount in the body during constant rate infusion using constant rate and first-order elimination in a drug showing single compartmental kinetics. In 1968, Kruger-Thiemer[39] published a mathematical approach for calculating infusion rates to reach and maintain a steady-state blood concentration of a drug described by 2 or more

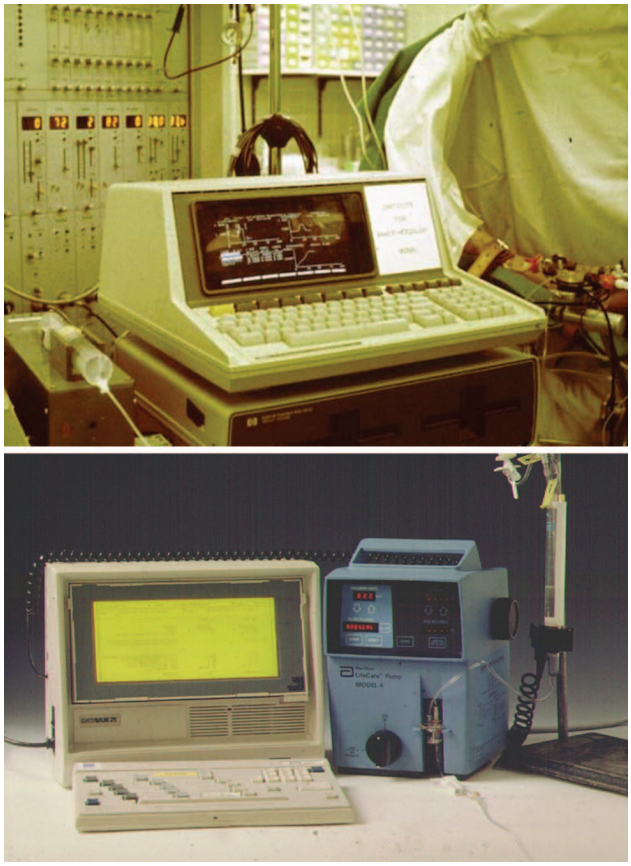

Figure 4. Top, Computer-assisted total IV anesthesia system (photograph courtesy of J. Schüttler, MD, Erlangen, Germany); Bottom, Computer-assisted continuous infusion II system using a Datavue 25 computer connected to an Abbott LifeCare pump Model 4 (photograph courtesy of T. Egan, MD, Utah).

compartments. Vaughan and Tucker[40,41] applied this model to a lidocaine infusion.

Schüttler and Schwilden performed the first TCI administration in Bonn, Germany, on May 1, 1979. In 1981, Schwilden[42] 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 (Fig. 4). They described the use of the BET scheme in a plasma-targeted TCI of etomidate (0.3 μg/mL) and alfentanil (0.45 μg/mL) to induce and maintain anesthesia. They concluded that CATIA provided adequate drug effect during anesthesia with a short recovery period.[43,44] In 1985, the Bonn group used CATIA to study the cerebral PDs of etomidate during linearly increasing predicted plasma concentrations of etomidate, the first use of TCI drug administration to quantify drug effects.[45,46] In 1988, the same group enhanced their software to administer propofol and alfentanil. They demonstrated that TCI provided a smooth induction without significant hemodynamic alterations, by good intraoperative titration, and rapid recovery.[6]

In Leiden, the Netherlands, Ausems and Hug[47] and Ausems et al.[48] were studying alfentanil PKs. Inspired by the work from the Bonn group, and supported by Janssen Pharmaceutica (Beerse, Belgium), they 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.[49] In 1988, the Leiden group used their alfentanil model to predict plasma concentrations during repeated bolus and variable rate infusions. The variability was similar to that of their TCI studies, demonstrating that PK variability has nothing to do with the infusion methodology but reflects the underlying biology.[50] In an additional study comparing plasma-controlled TCI administration of alfentanil with repeated bolus injections, Ausems et al. found that repeated bolus injections resulted in rapid fluctuations in alfentanil concentrations, which were not seen with TCI administration, an expected result. Although both methods controlled the patients' responses to noxious stimuli, the TCI group found a lower incidence of responsiveness, greater hemodynamic stability, and a somewhat lower incidence of side effects. They also used TCI as a tool to precisely quantify alfentanil concentration versus anesthetic effect relationships.[51]

Other groups were inspired by the research from Bonn and Leiden. In Bristol, United Kingdom, Tackley et al. developed a propofol TCI system using the BET approach based on the previously derived PKs from a propofol single-bolus study.[52] They found that blood concentrations were close to the predicted target.[7] A decade later, they incorporated ketamine into the device.[53]

As a visiting professor in Bonn in the early 1980s, Reves saw the work of Schüttler and Schwilden. On returning to the University of Alabama, Reves and Alvis developed CACI, a TCI system to titrate fentanyl and sufentanil during cardiac surgery.[35,54] CACI was written in PASCAL and was implemented on an Apple II Plus® computer (Apple, Cupertino, CA) that controlled an IMED 929® infusion pump (Carefusion, Basingstoke, UK). They applied a numerical approximation using a bilinear Z-transform of the differential equations.[35] This approach allowed approximate adjustment of the targeted plasma concentrations during infusion, which was not possible with the BET approach. Reves moved to Duke University and developed the CACI II system together with Jacobs (Fig. 4). This device consisted of a Datavue model 25 microcomputer connected to Abbott LifeCare model 4 infusion pumps. CACI II was programmed with PK models for fentanyl, alfentanil, sufentanil, midazolam, and propofol.[36,55] CACI II incorporated an enhanced algorithm for optimal linear-based control of the plasma concentration, developed by Jacobs.[36] Reves and coworkers used the CACI II prototype for many years in the late 1980s and 1990s at Duke University Medical Center, particularly to administer midazolam and fentanyl in cardiac surgery patients (Jerry Reves, MD, May 12, 2014, personal communication).

Don Stanski was similarly influenced by a sabbatical in Leiden, where he collaborated with Ausems and Lemmens in the TIAC studies. On returning to Stanford, Stanski recruited Steve Shafer to study PKs and specifically to investigate TCI. Shafer et al.[34] first evaluated the accuracy of the CACI I device and found various limitations. Unable to

Figure 5. Top, The STANPUMP TCI system using an MS-DOS-based PC connected to a Harvard Apparatus syringe pump (photograph courtesy of S. L. Shafer, MD, Stanford, CA). Bottom, Screenshot of the STELPUMP dual channel TCI system (photograph courtesy of J. Coetzee, MD, Stellenbosch, South Africa).

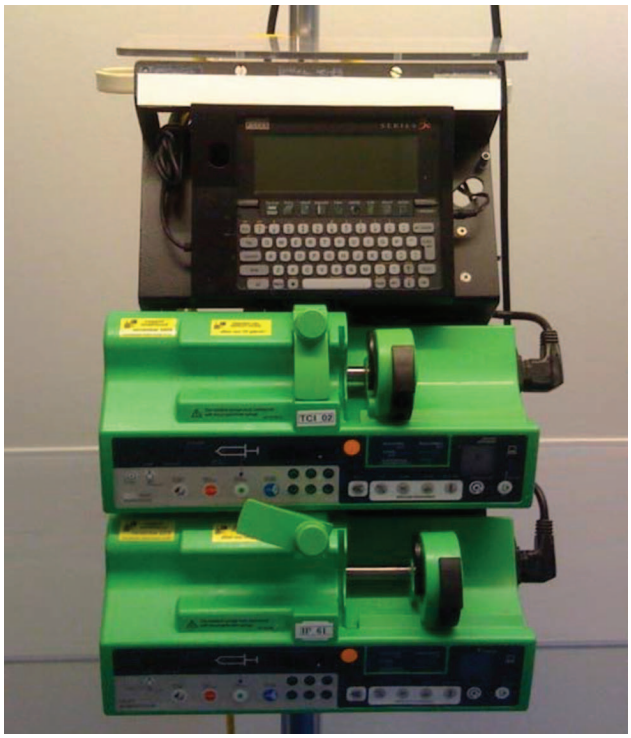

Figure 6. The Leiden target-controlled infusion system connected to 2 Fresenius syringe pumps (photograph courtesy of F. Engbers, MD, Leiden, The Netherlands).

use CACI II, Shafer developed STANPUMP (for STANford PUMP), written in C. STANPUMP was intended to be a generic program, and ran on any MS DOS-based computer. STANPUMP supported multiple infusion pumps, including the IMED 929, IMED C2 protocol, BARD Chronofusor, Harvard Pump 22, and the Graseby 3400 infusion pumps (Fig. 5). Initial versions of STANPUMP used Euler linear approximate of the differential equations (the approach used to transfer chocolates between boxes described earlier). The final version of STANPUMP uses an analytical solution to the 3-compartmental model to control plasma concentrations using TCI.[37] After 1993, the authors included the algorithms to rapidly achieve and maintain stable drug concentrations at the effect-site level allowing effect compartment-controlled TCI.[11] Effect-site control was a major step in providing precise titration of anesthetic drug effect. STANPUMP served as a testing environment for the implementation of other PK/PD principles, including application of the "Tpeak approach" to combining PK data from one study with PD data from another study,[31] the implementation of a maximum a posteriori probability Bayesian update of PK/PD parameters in real time from observations during drug administration,[56] the creation of detailed output files that could be directly incorporated into PK/PD estimating programs, the ability to read external files to use the PKs of any drugs, accommodation of multiple syringe sizes, and the ability to run from batch files, and command line-driven batch mode to facilitate clinical research (Steven L. Shafer, MD, June 5, 2014, personal communication). STANPUMP's PK/PD drug library contains models propofol, thiopental, methohexital, ketamine, etomidate, fentanyl, alfentanil, sufentanil, remifentanil, midazolam, diazepam, lorazepam, lidocaine, ketamine, rocuronium, vecuronium, atracurium, and pancuronium. As a research tool, it also has PKs for dogs, rats, horses, as well as humans. Shafer freely distributed STANPUMP, which explains why nearly half of the 559 studies in Appendix 1 of our accompanying article were conducted using STANPUMP.[4] Many of the principles implemented in STANPUMP, and even the code for the PK engine, were incorporated into subsequent implementations of research TCI systems and the commercially available Open TCI devices (Steven L. Shafer, MD, 2014, personal communication).

In Leiden, Jim Bovill continued the opioid pharmacology research conducted by Ausems. Because the TIAC device only allowed a 2 compartments, a new device was required for further research. Frank Engbers at Leiden University developed several TCI systems in the early 1990s. His first system used PC-based software connected to an IMED 929 and programmed in Turbo Pascal. This system was followed by a portable system comprising an Atari Portfolio palmtop computer driving 2 Ohmeda 9000 pumps and could be used to administer 2 drugs in TCI mode. These devices were used to study PD drug interactions.[57] This version was then followed by another portable system using a Psion 3A controlling 2 Fresenius or Graseby pumps (Fig. 6). The software was written in OPL and C. This system could do effect compartment-controlled TCI for only 1 pump because of limited capacity of the processor. The investigators further adopted this system TCI-patient-controlled-analgesia of alfentanil for postoperative pain with a safety loop back function using a respiration monitor.[58] One system is still in use at the authors' institution (Frank Engbers, MD, Leiden, March 4, 2014, personal communication).

At Glasgow University, White and Kenny developed an Atari-controlled propofol computer pump to deliver a specific targeted plasma concentration of propofol.[59] Roberts et al.[60] at Bristol suggested that 3 μg/mL was the right concentration for propofol.[61] They developed their own TCI prototype[60] using an Ohmeda 9000 pump connected to a Psion Organiser handheld computer.[62] Later the Psion organizer was replaced by a customized backbar containing a dual microprocessor control system and served as the prototype for the Diprifusor™ module (AstraZeneca, London, UK), the first commercial TCI device (see paragraph on Introduction of the Diprifusor). The Diprifusor module used 2 processors to solve the PK equations. The 8-bit processor used an Euler approximation for a parallel calculation of plasma concentration based on the movement of the motor, but the 16-bit processor uses a more complex algorithm. This was done to ensure a double check on the infused volume to guarantee safety. Because this was to be the first commercial implementation of a microprocessor infusion device, it was anticipated that regulatory authorities would be reassured by the presence of a second independent checking processor.

In the early 1990s, Johan Coetzee and Ralph Pina from Stellenbosch University, South Africa, developed STELPUMP (STELlenbosch PUMP), a TCI platform written in Borland's Turbo Pascal for MS DOS (Fig. 5). STELPUMP uses the Euler method's numerical approximation method to derive the plasma concentration[34] and the algorithm from Jacobs and Williams[63] to calculate the effect-site concentration. STELPUMP can control 2 syringe pumps simultaneously and is connectable to various syringe pumps such as the B. Braun Perfusor Secura pump, Harvard 22 syringe pump, Graseby 3400, and IVAC P4000. STELPUMP was one of the first programs offering a graphic interface. STELPUMP permitted users to specify PK parameter sets, maximum permissible plasma concentration (particularly important during effect-site targeted TCI), syringes brand and size, drug concentration, and infusion units. The data files from STELPUMP can be imported to a spreadsheet for graphing, etc. Coetzee made STELPUMP freely available for researchers. It has been used in various pharmacology studies[4] (Johan Coetzee, MD, March 21, 2014). As shown in Appendix 1 of the companion article,[4] STELPUMP has been particularly extensively used for studies in Asia.

Following the example of STANPUMP and STELPUMP, De Smet and Struys developed a modular computer-based TCI software called RUGLOOP (Fig. 7), written in C++ for Windows. The name RUGLOOP is a concatenation of *Rijksuniversiteit Gent*, the Flemish name of the University of Ghent, and"loop", as the system also served as the engine for their closed-loop drug administration system. RUGLOOP continues the tradition of STANPUMP and STELPUMP in being named for their host universities. The current release, RUGLOOP II is able to control multiple-syringe pumps simultaneously administering multiple drugs, targeting either the plasma or effect-site concentration. RUGLOOP II integrates the TCI software in a software platform capable of collecting vital signs from various monitors during research projects. RUGLOOP II uses analytically solved PK/PD algorithms similar to that of STANPUMP to calculate target plasma and effect-site concentration. In addition, RUGLOOP II serves as the engine for the closed-loop system for propofol administration using the bispectral index as a controlled variable.[64,65] RUGLOOP II also allows TCI-patient-controlled analgesia and TCI-patient-controlled sedation.[66] It is still actively used in research projects.[4]

Other research groups developed Windows-based, multichannel TCI software packages. In Erlangen, the pioneering group of Schüttler and Schwilden developed IVFEED (Fig. 7) allowing both plasma and effect-site TCI for multiple drugs. IVFEED uses the iterative analytical algorithm developed by Bailey and Shafer[37] to control the plasma concentration and an iterative analytical algorithm with forecasting similar to that described by Jacobs and Williams.[63] Aside from being able to maintain a specific target plasma or effect-site concentration, IVFEED can control a linearly increasing target concentration. The newest version of IVFEED allows TCI-patient-controlled analgesia. In 1999, researchers at the Facultad de Medicina Universidad de Chili developed AnestFusor using control plasma and effect-site concentrations during TCI (Fig. 8). AnestFusor has an extended drug library and can be connected to various syringe pumps. AnestFusor has been commercialized as ezFUSOR in Chili. More information can be found at http://www.smb.cl/ezFusor/indexen.html. Barvais and coworkers in Brussels, Belgium, developed various TCI software platforms over the past 25 years. The most recent version of their TCI software is called TOOLBOX (Fig. 8). Like RUGLOOP, TOOLBOX is a Windows program that can capture information from physiologic monitors, can perform closed-loop control based on the feedback from the monitors, and can control various commercially available infusion pumps.

INTRODUCTION OF THE DIPRIFUSOR TCI SYSTEM (EXCEPT IN UNITED STATES)

Propofol was launched in Europe in 1986. It was immediately apparent that propofol could be given by repeated injection or continuous infusion to maintain anesthesia, without incuring the long recovery seen with thiopental, the other IV-available hypnotic. A number of manually adjusted step-down infusion schemes for propofol infusion, generally in combination with an opioid analgesic or regional anesthesia, were described and achieved satisfactory results.[60,67,68] In 1990, the research department at ICI Pharmaceuticals hosted a meeting of the international groups who had developed research TCI systems (described earlier) to consider the possibility of commercializing TCI development. That preliminary meeting, coupled with a TCI symposium at the 1992 World Congress of Anaesthesiology in The Hague, convinced ICI that TCI could facilitate the use of propofol for maintenance of anesthesia. The development of the Diprifusor TCI system and associated technology has been described elsewhere[69–71] but will be summarized briefly here. Zeneca[b] decided not to manufacture TCI devices but rather to support independent medical devices companies interested in commercializing TCI technology. TCI is a drug-device combination, an uncommon application for regulatory authorities. The regulatory strategy was developed in discussions with regulatory authorities and interested device manufacturers. To ensure a standardized approach by different companies, ICI developed an electronics module incorporating one of

[b]The pharmaceuticals and agrochemicals divisions of ICI were divested as Zeneca from the parent company in 1992.

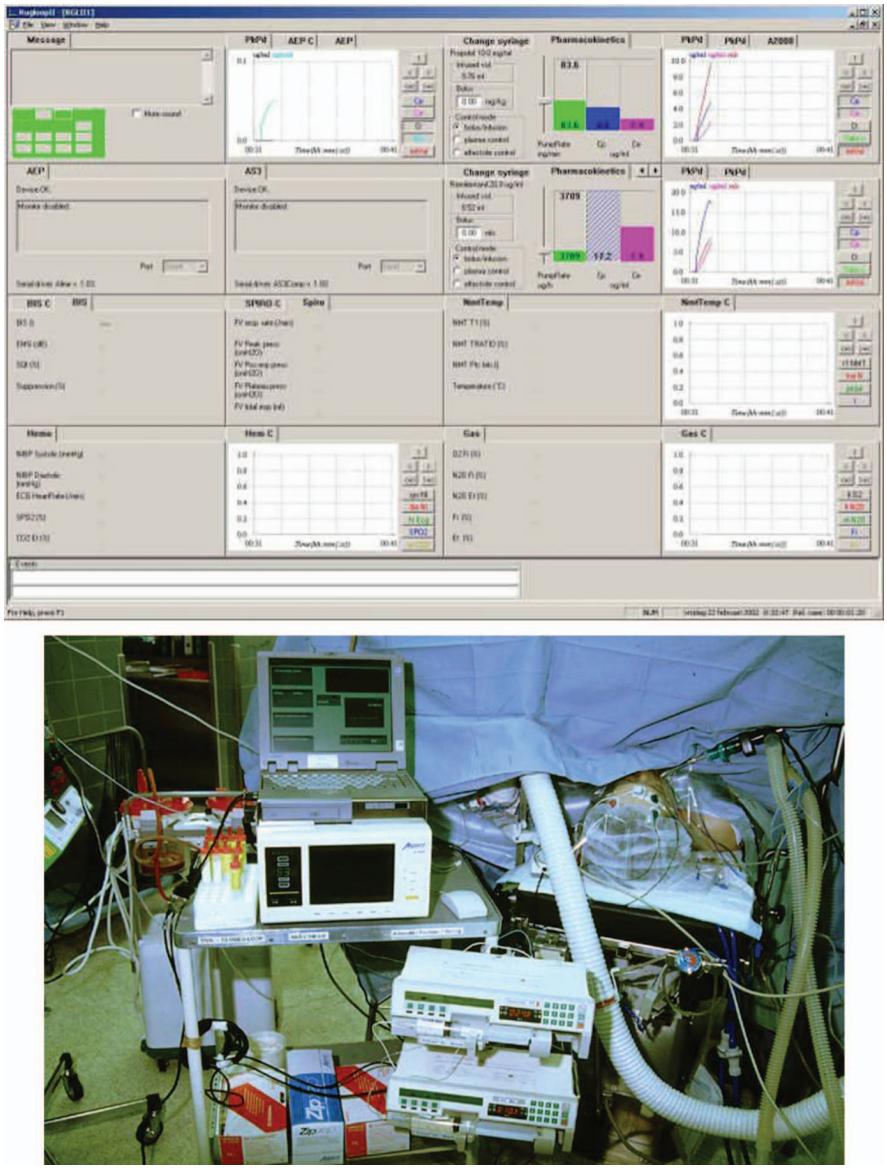

Figure 7. Top, Screenshot from RUGLOOP II (photograph courtesy of Tom De Smet, PhD, Temse, Belgium). Bottom, IV Feed TCI system connected to 2 B. Braun Perfusor syringe pumps (photograph courtesy of J. Schüttler, MD, Erlangen, Germany).

several available PK models[20] and infusion control software. The use of the Diprifusor module ensured standardized drug delivery for any TCI device. The PK model was selected based on the computer simulation studies,[69] a prospective comparative study of 3 models,[72] and discussions with academic groups. The Diprifusor control algorithms were developed by White and Kenny.[59] The control system used 2 microprocessors. The main 16-bit microprocessor implemented an exact mathematical solution, whereas the 8-bit microprocessor implemented a numerical approximate (the Euler method's solution, illustrated with the aforementioned chocolate model) to independently check the calculations.[70] The Glasgow group had significant clinical experience with this system, supplemented with 8 additional clinical trials in 428 patients sponsored by Zeneca to document the safety and efficacy of propofol administration by TCI. The studies also determined appropriate plasma-target settings for induction and maintenance of anesthesia, which were incorporated into the propofol label. Patients included in the program ranged in age from 16 to 83 years, with a weight ranging from 36 to 123 kg, ASA physical status I to III, undergoing gynecologic or orthopedic surgery, or major procedures expected to last for 3 to 6 hours, including major head and neck, abdominal, and neurosurgical procedures. Two studies involved patients undergoing coronary artery surgery. Efficacy assessments included induction times, hemodynamic effects, quality of anesthesia, and recovery times. Safety was assessed based on the frequency of reported side effects, which were consistent with previous experience with propofol.

Based on the studies, the propofol (Diprivan™, AstraZeneca) label was altered to include administration of propofol with a Diprifusor TCI system. The label also warned against TCI in children, based on the likelihood that adult PKs would poorly describe children.

The Diprifusor module requires the use of electronically tagged prefilled syringes containing propofol 1% or 2% injection. This prevents administration of other drugs or infusing the wrong concentration of propofol. Because propofol (Diprivan) labeling indicates that propofol may be

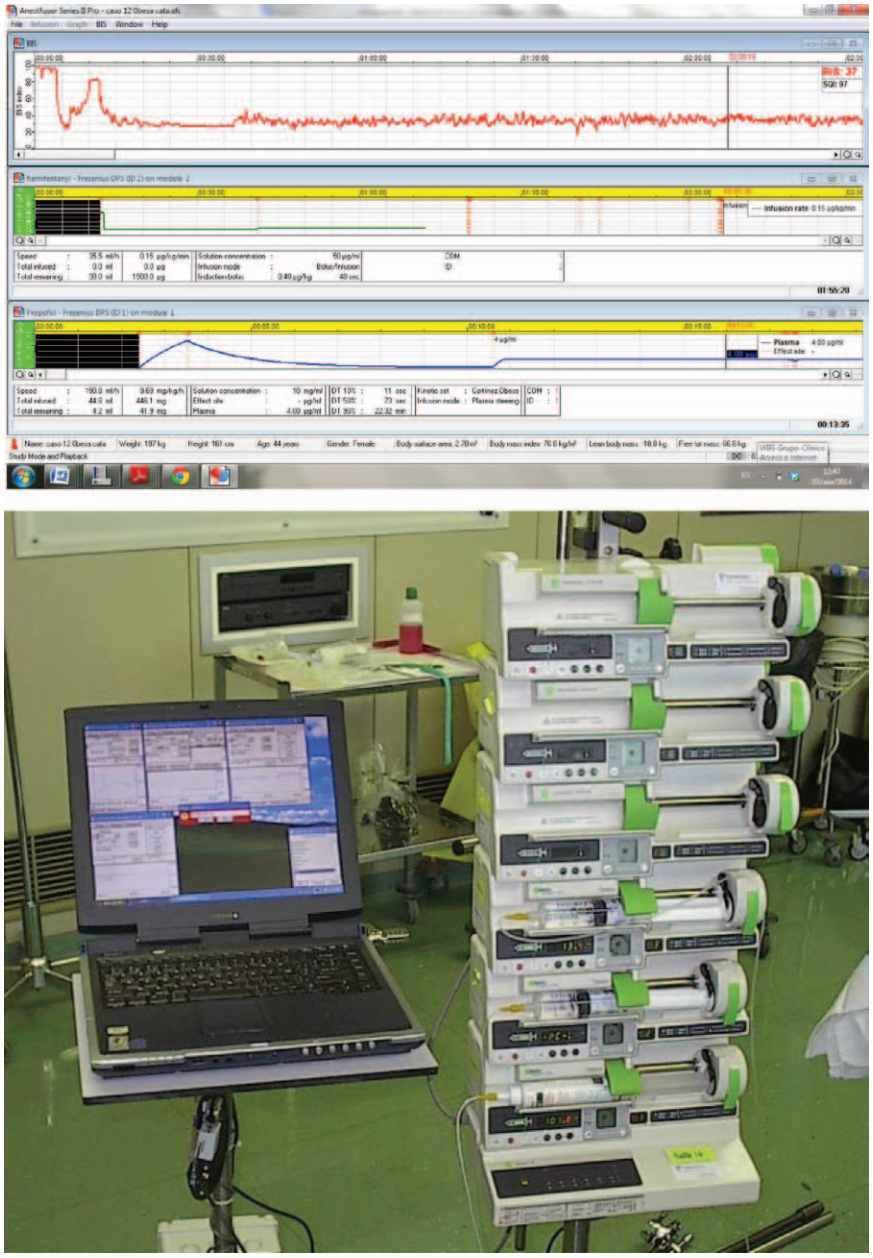

Figure 8. Top, Screenshot from AnestFusor (photograph courtesy of Andres Stutzin, Kristian Brinckmann, and Rodrigo Munoz, Santiago, Chili). Bottom, Toolbox software running on a laptop, steering multiple Fresenius pumps (photograph courtesy of L. Barvais, MD, Brussels, Belgium).

administered by TCI only with a Diprifusor system, a consequence is that product labeling for generic preparations of propofol does not provide guidance on administration of the drug by TCI.

The addition of TCI guidance to the prescribing information for Diprivan was approved in the United Kingdom, Austria, Norway, Spain, and Sweden in 1996. By the time of the Japanese submission in 1999 (approved 2001), further approvals had been obtained in Belgium, Brazil, Denmark, Eire, Finland, France, Germany, Greece, Holland, Luxembourg, Mexico, New Zealand, Portugal, Switzerland, and Venezuela. Currently, approvals for TCI administration using the Diprifusor module have been granted in >50 countries. A recent modification of the Diprifusor module to provide effect control with a k_{e0} of 0.6/min has been approved, but to date, amended labeling for this use has been obtained only in Germany.

Zeneca developed a comprehensive regulatory strategy to develop and commercialized the Diprifusor TCI system. In Europe, amended labeling for propofol was approved as a variation to the marketing authorization for propofol, subject to the approval of the Diprifusor TCI module and pumps incorporating the Diprifusor TCI module by a Notified Body acting under the auspices of the European Council directive 93/42/EEC concerning medical devices who granted a conformité européenne (CE) mark of conformity in 1996. The latter required Zeneca to complete a comprehensive program of TCI module software validation and to provide infusion pump companies with an integrated Diprivan TCI pump specification. Compliance with this specification ensured that all devices incorporating the Diprifusor TCI module would deliver propofol in a standard manner, specified as a precise infusion profile for specified target plasma propofol concentrations. The first CE marking for an infusion pump

Figure 9. Target-controlled infusion (TCI) pumps incorporating the Diprifusor module: Graseby 3500 syringe pump (Smiths Medical, Ashford, United Kingdom), Alaris IVAC P6000 TCI pump (Carefusion, Basingstoke, United Kingdom), Fresenius Master TCI pump (Fresenius, Bresins, France), and Terumo TE-372 syringe (Terumo, Tokyo, Japan; with permission from companies).

containing the Diprifusor TCI module was obtained in 1996 by Vial Medical, later acquired by Fresenius.

By 1997, the Diprifusor module had been incorporated in the Graseby 3500 syringe pump (Smiths Medical, Ashford, United Kingdom), the Alaris IVAC P6000 TCI pump (Carefusion, Basingstoke, United Kingdom), the Fresenius Master TCI pump (Fresenius, Bresins, France), and (later) the Terumo TE-372 syringe pump (Terumo, Tokyo, Japan; Fig. 9).

Zeneca sponsored local TCI courses to provide training TCI by local and international experts. These meetings involved lectures, including live video links to an operating theater where a Diprifusor TCI system was being used, and hands-on training with an infusion pump. The training included providing Diprifusor TCI systems to hospitals, analogous to the introduction of new inhaled agents by providing interested clinicians with calibrated vaporizers. Most of these pumps are still used clinically in various countries.

Two aspects of the Diprifusor TCI systems limited their continued acceptance. First, there was no ability to control the concentration at the site of drug effect. This reflected the introduction of effect-site control[11] after the basic design of the Diprifusor module had been settled.[59] The Diprifusor TCI systems could only administer Diprivan-branded propofol. Once generic propofol became available, clinicians wanted open TCI systems that could administer generic propofol, as well as other drugs (particularly remifentanil). Clinicians also wanted the additional precision of controlling the drug concentration at the site of drug effect. Gradually open TCI systems replaced Diprifusor TCI system in most countries. However, as the pioneering TCI platform, the Diprifusor TCI system and accompanying training program introduced TCI to routine clinical practice worldwide.

REGULATORY ODESSEY OF THE DIPRIFUSOR TCI SYSTEM IN THE UNITED STATES

In the United States, discussions with the Food and Drug Administration (FDA) began in 1993 when a blinded comparative study between standard infusions and TCI systems was requested by the agency. From the beginning, it was clear that the FDA was struggling to decide whether TCI should be handled by the drug division (the Center for Drug Evaluation and Research) or the device division (CDRH [the Center for Devices and Radiological Health]). The requested study was performed in the United States and aimed to compare induction time and the relative stability of hemodynamics and plasma propofol concentrations with TCI and a manually controlled infusion during induction and early maintenance in adult patients undergoing cardiac surgery. The study was a part of the submission report to the FDA but was not published as a scientific paper. Anesthesia was induced more rapidly in the TCI group. There was no difference between groups in the variability of measured plasma propofol concentrations and no clinically relevant differences in hemodynamic responses or safety assessments. These data were submitted with the European clinical and module validation data to support a Premarket Approval Application (PMA) to CDRH in 1995, followed by a PMA amendment demonstrating compliance of the Graseby 3500 pump incorporating the Diprifusor module with Zeneca's delivery performance specification. A prefilled syringe presentation of propofol had been produced. The FDA supported the proposal of Zeneca to use an electronic tag to confirm the presence and concentration of propofol in the syringe.

In 1996, the reviewers at the FDA changed, and the submission was transferred to Center for Drug Evaluation and Research as a supplement to the Diprivan New Drug Application, to be accompanied by approval of the Graseby pump incorporating a Diprifusor TCI module as a 510k Application (demonstration of equivalence) submitted to CDRH. The FDA sent Zeneca an approvable letter in 1997, but with an unacceptable requirement. Concerned about PK variability, the letter stated that the control dial for the pump be marked in ranges of 0.5 to 4, 1 to 8, and 2 to 16 μg/mL to

reflect PK variability. This implied, incorrectly, that the TCI pump was somehow responsible for PK variability. The following year the FDA accepted that this was an impractical approach and agreed that a label should simply point out that the actual plasma concentration differed from the target concentration because of PK variability. Additional safety updates and training plans were requested by the FDA, and answers were provided by Zeneca.

In 2000, the reviewers at the FDA changed again. The new team disagreed with earlier completed reviews. In 2001, the FDA issued a nonapprovable letter, considering the lack of precision in dosing posed an unacceptable risk. This occurred despite the concurrent extensive use of Diprifusor systems outside of the United States with no safety concerns. Assigning "blame" for PK variability to the TCI system, the FDA required a redesign of the TCI system. The FDA also requested further clinical trials to evaluate safety. In 2002, AstraZeneca[c] provided a response explaining that occasional outlying values of measured blood concentration were a consequence of PK variability and had not been associated with adverse events. Because the FDA had requested, Graseby submitted a 510k application for their TCI device. The FDA responded that there was no equivalent device marketed in the United States, upon which Graseby withdrew their 510K application.

By 2002, generic propofol was appearing in the market. The delays in FDA approval caused medical device companies to pursue open TCI systems for use outside of the United States. AstraZeneca was unwilling to initiate further clinical work with the Diprifusor TCI system in the United States. The New Drug Application submission was withdrawn in 2004, 9 years after initial submission to the FDA. In retrospect, the initial strategy suggested by the FDA that Zeneca pursue a PMA route would have been the most appropriate.

As long as the FDA insisted that TCI systems eliminate PK variability, an expectation not made of any other form of drug delivery, TCI had no path forward in the United States. Looking ahead, the mathematical proof that TCI systems necessarily have less variability than bolus injection[1] may open a path to approval of TCI systems in the United States not unnecessarily encumbered by the reality of PK variability.

OPEN TCI SYSTEMS

Starting in 2002, medical device companies introduced open TCI systems. In contrast to Diprifusor TCI systems, open TCI systems were not limited to propofol from one company. When using open TCI systems, the clinician selected a specific drug and a specific PK/PD model from the drug library incorporated in the device. Open TCI systems are also capable of targeting either plasma or effect compartment control mode. Carefusion (Basingstoke, United Kingdom) and Fresenius (Bresins, France) were the first companies launching an open TCI pump. Currently, various companies have commercialized open TCI systems. More details on the specific models and applications are described in our accompanying article.[4]

As with the pioneering Diprifusor TCI systems, the introduction of open TCI systems required a detailed regulatory strategy. A safe and effective product implies the product performs its task, with risks to the patient and the operator that are both well understood and satisfactorily mitigated. To accomplish this, potential hazards (technical errors, operator mistakes, and clinical hazards) are evaluated. Harmonized standards facilitate evaluation. Conformance to a standard provides a reference internally and to any third party that this part of the task was executed appropriately and/or this assembly of the device functions properly. The predominant guidelines are IEC60601 covering the technical aspects, ISO13485 handling the quality of design and manufacturing, and ISO14971 dealing with risk management.

In Europe, each medical device, including the open TCI systems, has to comply to the European medical device directive (MDD 93/42/CEE) to carry the mandatory CE mark. For all except the least risk-sensitive medical devices, MDD requires a notified body (e.g., TUV, LNE-GMed, SGS) to assess conformity to the relevant standards of all stages from design to postmarketing. This assessment is reasonably efficient because of harmonized standards. There is alternative mandatory conformity marking for medical devices in other parts of the world (e.g., the Pharmaceutical Affairs Law in Japan).

In accordance to the aforementioned data, the open TCI systems are evaluated both for their technical performance and clinical accuracy. The clinical evidence of the applied model and the accurate range of plasma and effect-site concentration targets relies on publications in the scientific literature. Published models have been embedded in the pumps for propofol in adults[20,25,26,73] and children,[27,74] remifentanil,[23,24] sufentanil,[22] and alfentanil.[19,75] More details can be found in our accompanying review of TCI global use.[4]

The technical verification ensures that, on top of the MDD requirements for general-purpose infusion pumps as mentioned earlier, open TCI systems will apply an infusion profile and predict a concentration sufficiently close to what a pure theoretical implementation of the selected clinical model would realize. Because the open TCI systems are physical devices, this requires extensive evaluation and simulation of long-term stability, absolute momentary accuracy of the delivered dose, and absence of rounding noise-induced oscillations under all clinical situations for each model implemented. Pure theoretical implementation includes modeling expected PK variability intrinsic to the drug and patient population selected.

When the device is commercialized, each company has to set up a Plan-Do-Check-Act Quality Insurance System using detailed Standard Operating Protocols as described in the MDDs to document and categorize all reported device errors or clinical complaints. If a serious product performance report is filed, a recall or an immediate global update of the device can become mandatory. More details can be found in our accompanying TCI safety review article.[5]

Most global or national notified bodies granting market approval for the open TCI systems did not request additional accuracy studies covering the interpatient variability in relation to the population model. They considered the extensive literature describing PK performance of the devices, including that the expected PK variability was

[c]After further divestment of the agrochemicals division of Zeneca, the remaining Zeneca Pharmaceuticals division of Zeneca merged with Astra to form AstraZeneca in 1999.

accurate.[1] Neither did they request an update of the drug insert labels covering the use of TCI. An exception of the above can be found in Japan. A requirement for an alteration in the Diprivan label is the reason that only Diprifusor TCI systems are available in Japan today.

In 2008, a Cochrane review by Leslie et al.[3] compared TCI systems versus manually controlled infusion. The review mostly included studies with Diprifusor TCI systems. The authors found no significant difference between 2 types of anesthetic drug delivery with respect to quality of anesthesia, recovery, or adverse events.

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. These populations were not included in most of the original studies generating the values for the current clinically available models. As a result, extrapolations outside the original studied population reduce the accuracy of the models.[76] For example, Eleveld et al.[77] published a general purpose propofol PK model using data made available by various research groups. Similar projects should be initiated for other drugs in the future, with research funding to support these collaborative efforts. 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.[d]

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 various benzodiazepines) to be added, companies are continuously monitoring the possibilities. Hereby, better interaction among the pharmaceutical companies, device manufacturers, and the device and medicines regulatory agencies should be encouraged to provide consistent standards for the PK models for the same drug.

Connectivity of medical equipment remains a significant problem in anesthesia. Communication protocols between open TCI systems and other medical devices should be standardized. This will open the possibility to combine plasma and effect-site concentration calculated by the TCI devices with PD measures such as depth of anesthesia monitors into a single advisory display. Ultimately, this could lead to a more general use of closed-loop systems for drug administration.[17] Finally, 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. Linking TCI drug delivery to anesthesia information management systems, enhancing the computerized safeguards for anesthesia care, may represent the important safety potential of TCI anesthetic drug delivery systems.

[d]http://www. opentci.org/doku.php?id=industry:fk:fk.

DISCLOSURES

Name: Michel M. R. F. Struys, MD, PhD, FRCA (Hon).
Contribution: This author attests to the integrity of the original data and helped write the manuscript.
Attestation: Michel M. R. F. Struys approved the final manuscript.
Conflicts of Interest: Michel M. R. F. Struys is co-owner of RUGLOOP, a software program for target-controlled infusion. His department has received non-restrictive educational grants and fees for consultancy and advice in the field of medical device technology from Dräger Medical (Lübeck, Germany), Fresenius Kabi (Germany), Baxter (Chicago, United States), Sphere Medical (United Kingdom). He is an editor of the *British Journal of Anaesthesia*.
Name: Tom De Smet, PhD.
Contribution: This author attests to the integrity of the original data and helped write the manuscript.
Attestation: Tom De Smet approved the final manuscript.
Conflicts of Interest: Tom De Smet is co-owner of RUGLOOP, a software program for target-controlled infusion and owns the medical engineering company Demed, Temse, Belgium. He has received fees for consultancy from Carefusion and Fresenius Kabi.
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Contribution: This author attests to the integrity of the original data and helped write the manuscript.
Attestation: John (Iain) B. Glen approved the final manuscript.
Conflicts of Interest: John (Iain) B. Glen is a former employee of ICI, Zeneca, and AstraZeneca (retired 2000) and was closely involved in the clinical validation and commercial development of the Diprifusor TCI system. He was an owner and a director of Glen Pharma Ltd, which traded as a Consultancy between 2000 and 2010, and worked with AstraZeneca, GlaxoSmithKline, NeuroSearch, Labopharm, Claris Life Sciences, Carefusion, and Fresenius Kabi. Since 2010, he has been paid by Anaesthesia Technology Limited for documentation relating to Diprifusor development.
Name: Hugo E. M. Vereecke, MD, PhD.
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Attestation: Anthony R. Absalom approved the final manuscript.
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