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Target-Controlled Drug Delivery

Progress toward an Intravenous "Vaporizer" and Automated Anesthetic Administration

Talmage D. Egan, M.D.

CURRENTLY, anesthesiologists routinely use a variety of sophisticated devices for the delivery of IV drugs. The gravity-driven infusion systems in widespread use just a few years ago are primitive compared with the convenience, accuracy, and precision provided by today's calculator pumps. However, although modern infusion systems are remarkably advanced, they still fall short of the convenience and theoretical appeal associated with the delivery of inhaled anesthetics by an agent-specific vaporizer. Emulation of the clinical convenience and pharmacokinetic-dynamic control provided by vaporizers is perhaps the ultimate goal in the development of infusion devices for IV anesthetics.

The aim of this brief review is to contrast IV *versus* inhaled anesthetic delivery systems, develop the concept of the computer-controlled infusion pump as an "intravenous vaporizer," and survey the current state of the art in computer-controlled IV drug delivery.

Intravenous *versus* Volatile Delivery Systems

Drug Delivery via *a Vaporizer*

Administering volatile anesthetic through the lung *via* a calibrated vaporizer affords several fundamental advantages that are a function of gaining access to the circulation *via* the lung. Because of the equilibration between the alveolar and pulmonary capillary partial pressures, the partial pressure of an inhaled anesthetic in the blood and at the site of drug action approaches the setting on the vaporizer as anesthetic administration continues. This enables impressively accurate drug administration; the clinician can set a partial pressure above which the blood concentration will not increase. Moreover, the expired concentration target can be measured with respiratory gas analysis, providing pharmacokinetic confirmation. Finally, the clinical meaning of the measured concentration is well described and understood in terms of minimum alveolar concentration (MAC), providing an element of pharmacodynamic control. Clinicians know and understand MAC; in conducting an anesthetic they think in terms of delivering the appropriate MAC fraction (or multiple) for a given patient, operation, and anesthetic technique.

Drug Delivery via *a Calculator Pump*

In contrast, when access to the circulation is gained directly, there is nothing to prevent the continual uptake of drug. Thus, without the aid of a computer model, the infusion rate of an IV anesthetic does not reveal much about the resulting concentration in the blood, preventing concentration-targeted administration. Furthermore, there is no capability to measure the concentration of IV anesthetics in real time, preventing pharmacokinetic confirmation equivalent to that when using a vaporizer for inhaled anesthetics. Finally, even if concentrations of IV drugs were measurable in the clinical setting, the meaning of a given concentration is not widely understood; that is, a thoroughly researched and widely appreciated analog of MAC for IV drugs is not yet fully developed. Clinicians in some parts of the world (most notably the United States and Canada) are not accustomed to thinking in terms of the appropriate target concentration of IV drug instead of an appropriate infusion rate. Thus, current calculator pumps, although accurate and sophisticated, fall short of the theoretical appeal and practical convenience associated with the delivery of volatile anesthetics *via* the lung.

Computer-controlled Drug Delivery as an Intravenous Vaporizer

Basic Concept. Target-controlled infusion (TCI) systems deliver IV drugs according to the drug's pharmacokinetic behavior using an infusion pump controlled by a computer. As illustrated in figure 1, based on the drug's typical pharmacokinetic behavior (as characterized by a population pharmacokinetic model constructed from a clinical pharmacology study), the computer pump control algorithm calculates the infusion rate that is neces-

Associate Professor of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah.

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Address reprint requests to Dr. Egan, Department of Anesthesiology, University of Utah Health Sciences Center, 30 North 1900 East, Salt Lake City, Utah 84132. Address electronic mail to: talmage.egan@hsc.utah.edu.

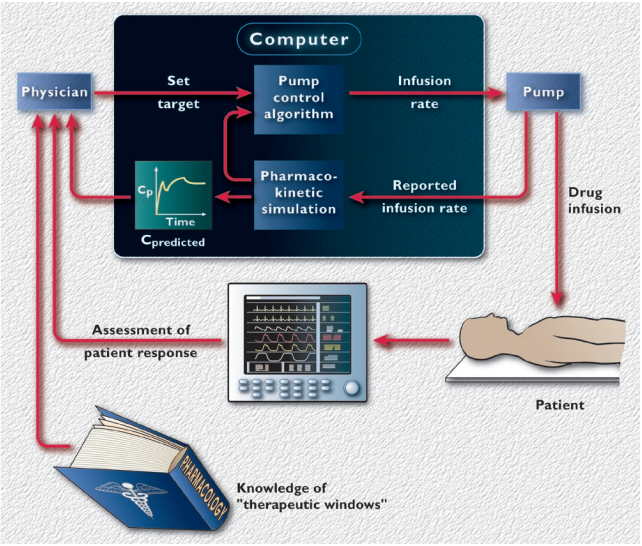

Fig. 1. Schematic representation of a TCI system for anesthetic drugs. According to knowledge of therapeutic windows, patient response, and the current prediction of drug concentration ($C_{predicted}$), the physician sets the anesthetic drug concentration target. Using a pharmacokinetic model for the drug, the computer calculates the appropriate infusion rates over time to achieve and maintain the target concentration and directs the infusion pump to administer the appropriate amount of drug. The pump reports to the computer the amount of drug administered to the patient so that the computer's pharmacokinetic simulation of the current drug concentration can be updated and confirmed (see text for details).

sary to achieve a user-designated drug concentration (the "target") in the bloodstream. After calculating the infusion rate, the computer directs the infusion pump to administer the appropriate dosage of drug. Because the drug accumulates in the body, the computer frequently recalculates the appropriate dosage based on the computer's pharmacokinetic simulation of the current drug concentration ($C_{predicted}$) in the bloodstream. In this way, the computer's prediction of the current drug concentration serves as continuous input to the computer's pump control algorithm.

TCI pumps make progress toward the concept of a "vaporizer" for IV drugs because they address the fundamental limitation associated with delivering drugs directly into the circulation.[1] Constant-rate infusions result in continuous drug uptake. TCI pumps, in contrast, gradually decrease the rate of infusion based on the drug's pharmacokinetics.

Although TCI systems use complex mathematical models to compute the drug dosage,[2] in general terms the dosage regimen is patterned after the Bolus-Elimination-Transfer (BET) method first described by Kruger-Thiemer.[3,4] This method relies on an initial bolus (the *B* of BET) to achieve the target concentration, a continuous infusion to replace drug that has been eliminated (the *E* of BET) and an exponentially decreasing infusion to replace the drug that is transferred (the *T* of BET) to peripheral tissues. The infusion rates are updated frequently (as often as every 10 s), depending on the predictions of the pharmacokinetic model and any changes in the target concentration set by the user.

A unique feature of TCI systems is that they can account for demographic, physiologic, or disease state covariates (*i.e.*, patient characteristics) that alter drug disposition. For example, if a given pharmacokinetic study has shown that age, body weight, or gender alter drug clearance or distribution, this influence is incorporated into the pharmacokinetic model used by the TCI system. The influence, if known, of physiologic covariates such as kidney or hepatic function and disease states such as congestive heart failure can also be incorporated into the models. When a covariate alters an individual pharmacokinetic parameter, it is impossible to make adjustments for this kinetic alteration fully when using calculator pumps (*i.e.*, the covariate influences the dosage scheme in a very complex way); this is a distinct advantage of TCI systems.

Delivery of drug *via* a computer-controlled infusion pump requires a different knowledge base of the physician. Rather than setting an infusion rate based on clinical experience and literature recommendations, the anesthesiologist using a TCI system designates a target concentration and the computer calculates the infusion rates necessary to achieve the concentration over time. Successful use of a computer-controlled infusion pump thus requires that the user think in terms of, and specify, the appropriate therapeutic concentration rather than the appropriate infusion rate.

In setting the target, the anesthesiologist relies on three sources of information, as shown in figure 1. The initial target is set on the basis of knowledge of the drug's therapeutic windows in the context of a specific patient (*e.g.*, patient demographic features and medical condition) and a procedure (*e.g.*, type and level of noxious stimulation). Subsequent adjustments to the target are made on the basis of patient response and the predicted drug concentration.

TCI Nomenclature. Drug delivery by a computer-controlled pump according to a pharmacokinetic model has been referred to by a variety of names in the anesthesia literature. Known variously as computer-controlled infusion pump (CCIP), computer-assisted continuous infusion (CACI), target-controlled infusion (TCI), computer assisted titration of IV anesthesia (CATIA), and model-based drug delivery, all of these methods of computer-controlled delivery are "open-loop," in that no feedback from the patient is automatically considered by the pump infusion-control mechanism. The computer prediction of the current drug concentration is the only feedback evaluated by the pump. The anesthesiologist must assess the adequacy of patient response and change the target concentration as necessary. In recent years, TCI has emerged as the consensus, preferred nomenclature for open-loop devices.[5]

"Closed-loop" computer-controlled drug delivery is fundamentally different in that 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). For both open- and closed-loop infusers, the computer's control algorithm considers differences between the target and the feedback signal and generates a "control signal." This control signal alters the pump behavior to achieve the desired target.

TCI Performance. TCI systems report a predicted concentration for the drug of interest. Because the TCI system predicts the concentration on the basis of the drug's typical pharmacokinetic behavior (*i.e.*, population pharmacokinetics), there is always a discrepancy between the predicted concentration and the actual concentration in the individual patient. It is important for the TCI user to understand that the predicted concentration reported by the TCI system is only an estimate. To use TCI systems intelligently, the user must have some sense of the accuracy of the predicted concentration.

Varvel *et al.*[6] defined four parameters that are useful in the assessment of TCI performance; all of these parameters are based on the Percentage Performance Error (PE), which is defined as:

$$PE = \frac{Cm - Cp}{Cp} \times 100$$

where Cm is the measured (actual) concentration and Cp is the predicted concentration. The Median Absolute Performance Error (MDAPE) is the median PE of the TCI system and is a measure of how close the predicted concentration is to the measured concentration (*i.e.*, accuracy). A MDAPE of 20% would mean that half of the predictions would be within 20% or closer to the targeted value and half would be outside that range. The Median Prediction Error (MDPE) is a measure of the overall bias of the predictions; it indicates whether the TCI system systematically overshoots or undershoots the target. Divergence and wobble, the other two performance parameters, are measures of how the accuracy changes over time (how much it diverges) and how variable the performance is over time (how much it wobbles). These two parameters are important when the TCI system is used for prolonged periods (*i.e.*, many hours to days, such as in an intensive care unit setting).[6] The four TCI performance parameters described by Varvel *et al.* are calculated for individual subjects and then summarized across an entire population.

When these performance measures are applied to a wide variety of TCI systems (*i.e.*, different software and hardware), the typical prediction error (MDAPE) ranges from approximately 15–30% and the typical bias (MDPE) ranges from 3–20%, although the bias should be very nearly zero when optimal kinetic parameter sets are used.[7–9] Interestingly, presumably because of intrasubject variability, programming a TCI system with an individual's personal pharmacokinetic parameters in research settings (this, of course, requires a separate study to estimate the individual's parameters) does not improve TCI performance dramatically.[10,11] Figure 2 is an example of typical TCI performance for the opioid fentanyl, showing the best, median, and worst performance when the system was used in 21 subjects. As demonstrated in figure 2, on average the performance of the system is quite good, although some subjects are, obviously, poorly characterized by the population pharmacokinetic model.

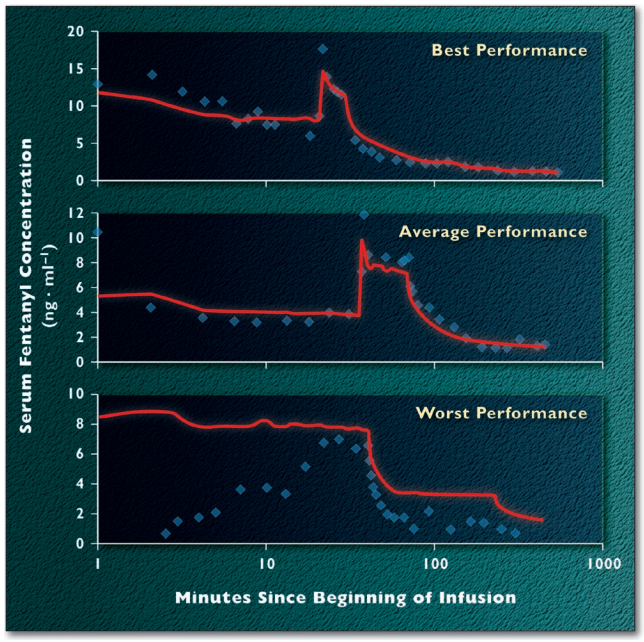

Fig. 2. The best, median, and worst performance of a TCI system when used to administer fentanyl to 21 patients. The *lines* represent the predicted concentrations, and the *diamonds* represent the measured concentrations. Reprinted with permission from Shafer *et al.*[8]

Also, with regard to pharmacologic variability and TCI performance, it should be emphasized that pharmacologic variability is a function of biology, not technology. A TCI system neither amplifies nor reduces any underlying pharmacokinetic variability, except to the extent that a TCI system may reduce interpatient variability by calculating the influence of covariate effects (*e.g.*, the effect of age and weight) on the pharmacokinetics. TCI systems can also reduce the time-dependent variability in concentration that necessarily occurs with constant rate infusions because of drug accumulation.

Problems and Controversies with TCI Systems. There are some important unsolved problems, limitations, and controversies surrounding TCI systems. The most obvious limitation is that TCI systems can only be as good as the pharmacokinetic model with which they

are programmed. It is clear that some pharmacokinetic parameter sets for a given drug perform better than others when used to deliver a drug by computer. Which pharmacokinetic model parameter sets perform best and why is an area of intense investigation.[12]

Other TCI controversies relate to the problem of plasma-effect site dysequilibrium. This is an important issue in that the effect site, or "biophase" concentrations, not the plasma concentrations, best correlate with drug effect. Although the plasma has been the target site for most early TCI applications, the effect site is the more logical target.[13,14] When targeting the plasma concentration, there is a significant delay in the achievement of a stable level of drug effect for many drugs; targeting the effect site results in faster attainment of therapeutic concentrations in the biophase, although this advantage may be associated with a slightly greater incidence of adverse events (*e.g.*, hypotension).[13]

Another unresolved problem associated with TCI is the search 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.). How IV anesthetic CP_{50}s estimated from such diverse circumstances can be rationally applied to the selection of TCI targets for a given operation and anesthetic technique is not well understood. It is clear that the typical clinician has much more familiarity with MAC than with this much more diverse IV anesthetic CP_{50} data.

An important controversy surrounding TCI in the United States (and elsewhere, including Canada) relates to regulatory rather than scientific issues. The U.S. Food and Drug Administration has guidelines regarding combination products, but because TCI technology is a device inseparably connected to a drug, complexities arise in terms of whether the technology ought to be regulated as a drug or as a device. The lack of precedent for TCI system approval in the United States no doubt represents a significant obstacle to the commercial development of the technology. The uncertainty of the regulatory issues surrounding TCI in the United States likely prevents capable companies from being sufficiently motivated to pursue development of TCI technology for the U.S. market as they have in other countries. Although many North American–based clinician-scientists have played important roles in the development of TCI concepts and technology,[8,15] TCI technology is still restricted to the research domain in the United States. This is perplexing from a scientific perspective because TCI systems deliver approved drugs in approved doses *via* approved routes for approved indications, perhaps with improved safety and efficacy, although almost certainly with no worse.

Current TCI State of the Art

Clinical Applications. TCI is actually a well-established technology that has been used in research and clinical care for many years. The first description of a TCI system dates to the early 1980s, when Schwilden *et al.* developed a TCI system to infuse etomidate and alfentanil to provide anesthesia for gynecologic surgery.[16,17] Since then, a wide variety of TCI devices have been produced to infuse an array of drugs, including sedatives, analgesics, and muscle relaxants.[18–20] Perhaps because of its short-acting pharmacokinetic profile, propofol has become the most often-infused drug by TCI.

A proprietary propofol TCI system has now been in widespread clinical use in the majority of developed countries for over 6 yr.[21,22] Over 17,000 of these systems have been used for an estimated 13 million patients (personal written communication, May 6, 2003, John (Iain) B. Glen, Ph.D., Glen Pharma Ltd., Cheshire, United Kingdom). With the exception of a technical issue relating to a specific manufacturer's pump hardware (not the TCI software) that led to the under-delivery of propofol and intraoperative awareness in a small number of cases,[23] reports raising safety concerns about the technology have not appeared in the literature.

TCI systems have also been well received in clinical settings outside the operating room. For example, propofol TCI systems have now been extended beyond their use for general anesthesia to the conscious sedation/analgesia domain with promising results.[24] A TCI system using alfentanil has been applied to patient-controlled analgesia management of postoperative pain (when the user indicates inadequate pain relief by pressing the "button," the alfentanil target is increased).[25] TCI systems have also been applied to the sedation of mechanically ventilated patients.[20]

There is evidence that TCI systems can improve certain outcomes (*e.g.*, intraoperative hemodynamics, the need for reversal agents, the speed of recovery),[26–29] although it has been difficult to demonstrate a truly compelling outcome improvement with the technology. Interestingly, most users tend to prefer TCI systems to manual infusions.[30] If and until large outcome trials demonstrate a clear improvement in outcome through using TCI, in the clinical setting the technology is probably best viewed as an incremental advance and not as truly revolutionary.

Research Applications. Although it is perhaps still unclear exactly what role computer-controlled drug delivery will play in clinical anesthesiology 10–20 yr in the

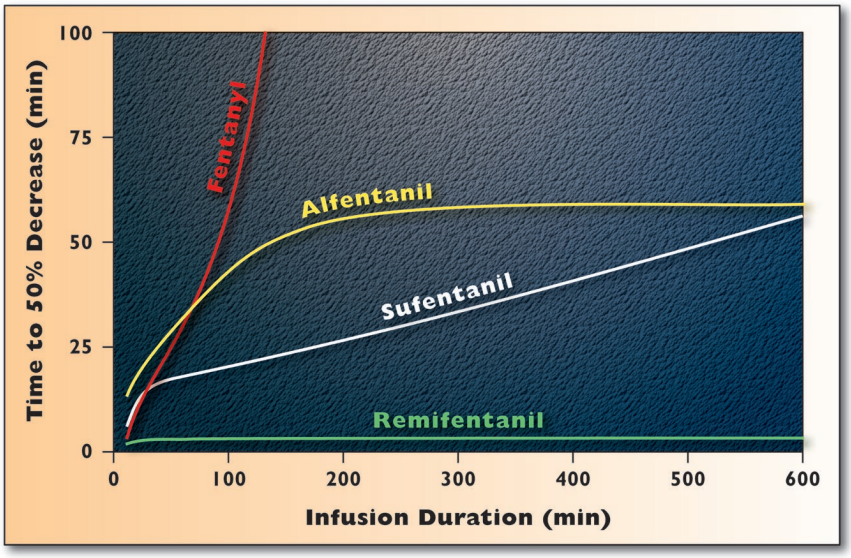

Fig. 3. The context-sensitive half-times of the currently marketed fentanyl congeners. Defined as the time required to achieve a 50% decrease in concentration after termination of a continuous infusion targeted to maintain a steady-state concentration, the context-sensitive half-time has been used to compare the clinical behavior of individual drugs within a selected drug class. The context-sensitive half-time is a TCI simulation (see text for details). Reprinted with permission from Egan *et al.*[34]

future, its position in clinical pharmacology research is now already solidified. It is impossible to make meaningful pharmacodynamic observations without controlling the pharmacokinetic aspects of an experiment. TCI systems enable the investigator to establish a steady-state concentration of drug very near a target concentration so that pharmacodynamic measurements can be made without concern that drug levels are rapidly changing or are out of the intended range. Using TCI systems for pharmacokinetic control of a pharmacodynamic experiment has become a frequently applied and indispensable method in anesthesia clinical pharmacology research.[10,31,32]

Another firmly entrenched research application of TCI systems is the use of simulation, requiring only the software of a TCI system, not the hardware. Through simulation of TCI drug delivery, it is possible to make comparisons about the clinical pharmacology of two drugs that are not possible in any other way. The context-sensitive half-time is just one example of TCI simulation.[33] Defined as the time required to achieve a 50% decrease in concentration after termination of a continuous infusion targeted to maintain a steady-state concentration, the context-sensitive half-time has been used to compare the clinical behavior of individual drugs within a selected drug class. Figure 3 illustrates the context-sensitive half-times of the fentanyl congeners.[34] The context-sensitive half-time has important implications in terms of rational drug selection and administration in anesthesiology.[35] TCI simulation software can be downloaded from a number of sites on the internet (*e.g.*, http://anesthesia.stanford.edu/pkpd, http://www.anesthesia-uzgent.be/rugloop.htm, accessed June 15, 2003.)

References

1. Egan TD: Intravenous drug delivery systems: Toward an intravenous "vaporizer." J Clin Anesth 1996; 8(suppl 3):8S–14S

2. Bailey JM, Shafer SL: A simple analytical solution to the three-compartment pharmacokinetic model suitable for computer-controlled infusion pumps. IEEE Trans Biomed Eng 1991; 38:522–5

3. Kruger-Theimer E: Continuous intravenous infusion and muticompartment accumulation. Eur J Pharmacol 1968; 4:317–24

4. Schwilden H: A general method for calculating the dosage scheme in linear pharmacokinetics. Eur J Clin Pharmacol 1981; 20:379–86

5. Glass PS, Glen JB, Kenny GN, Schuttler J, Shafer SL: Nomenclature for computer-assisted infusion devices. Anesthesiology 1997; 86:1430–1

6. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 1992; 20:63–94

7. Ausems ME, Stanski DR, Hug CC: An evaluation of the accuracy of pharmacokinetic data for the computer assisted infusion of alfentanil. Br J Anaesth 1985; 57:1217–25

8. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology 1990; 73:1091–102

9. Glass PS, Jacobs JR, Smith LR, Ginsberg B, Quill TJ, Bai SA, Reves JG: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. Anesthesiology 1990; 73:1082–90

10. Fiset P, Lemmens HL, Egan TE, Shafer SL, Stanski DR: Pharmacodynamic modeling of the electroencephalographic effects of flumazenil in healthy volunteers sedated with midazolam. Clin Pharmacol Ther 1995; 58:567–82

11. Hill HF, Saeger L, Bjurstrom R, Donaldson G, Chapman CR, Jacobson R: Steady-state infusions of opioids in human volunteers: I. Pharmacokinetic tailoring. Pain 1990; 43:57–67

12. Mertens MJ, Engbers FH, Burm AG, Vuyk J: Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia. Br J Anaesth 2003; 90:132–41

13. Jacobs JR, Williams EA: Algorithm to control "effect compartment" drug concentrations in pharmacokinetic model-driven drug delivery. IEEE Trans Biomed Eng 1993; 40:993–9

14. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm 1992; 20:147–69

15. Glass PS, Reves JG: Drug delivery system to improve the perioperative administration of intravenous drugs: Computer assisted continuous infusion (CACI). Anesth Analg 1995; 81:665–7

16. Schwilden H, Schuttler J, Stoekel H: Pharmacokinetics as applied to total intravenous anaesthesia: Theoretical considerations. Anaesthesia 1983; 38(suppl):51–2

17. Schuttler J, Schwilden H, Stoekel H: Pharmacokinetics as applied to total intravenous anaesthesia: Practical implications. Anaesthesia 1983; 38(suppl): 53–6

18. Jaklitsch RR, Westenskow DR, Pace NL, Streisand JB, East KA: A comparison of computer-controlled versus manual administration of vecuronium in humans. J Clin Monit 1987; 3:269–76

19. Schuttler J, Kloos S, Schwilden H, Stoeckel H: Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 1988; 43(suppl):2–7

20. Somma J, Donner A, Zomorodi K, Sladen R, Ramsay J, Geller E, Shafer SL: Population pharmacodynamics of midazolam administered by target controlled infusion in SICU patients after CABG surgery. Anesthesiology 1998; 89:1430–43

21. Glen JB: The development of "Diprifusor": A TCI system for propofol. Anaesthesia 1998; 53(suppl 1):13–21

22. Kenny GN, White M: Intravenous propofol anaesthesia using a computerised infusion system. Anaesthesia 1991; 46:156–7

23. Laurent S, Fry R, Nixon C: Serial failure of Diprifuser infusion pumps. Anaesthesia 2001; 56:596–7

24. Church JA, Stanton PD, Kenny GN, Anderson JR: Propofol for sedation during endoscopy: Assessment of a computer-controlled infusion system. Gastrointest Endosc 1991; 37:175–9

25. Van den Nieuwenhuyzen MC, Engbers FH, Burm AG, Vletter AA, Van Kleef JW, Bovill JG: Target-controlled infusion of alfentanil for postoperative analgesia: A feasibility study and pharmacodynamic evaluation in the early postoperative period. Br J Anaesth 1997; 78:17–23

26. Ausems ME, Vuyk J, Hug CC Jr, Stanski DR: Comparison of a computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. ANESTHESIOLOGY 1988; 68:851–61

27. De Castro V, Godet G, Mencia G, Raux M, Coriat P: Target-controlled infusion for remifentanil in vascular patients improves hemodynamics and decreases remifentanil requirement. Anesth Analg 2003; 96:33–8

28. Passot S, Servin F, Allary R, Pascal J, Prades JM, Auboyer C, Molliex S: Target-controlled versus manually controlled infusion of propofol for direct laryngoscopy and bronchoscopy. Anesth Analg 2002; 94:1212–6

29. Struys MM, De Smet T, Versichelen LF, Van De Velde S, Van den Broecke R, Mortier EP: Comparison of closed-loop controlled administration of propofol using Bispectral Index as the controlled variable versus "standard practice" controlled administration. ANESTHESIOLOGY 2001; 95:6–17

30. Servin FS: TCI compared with manually controlled infusion of propofol: A multicentre study. Anaesthesia 1998; 53(suppl 1):82–6

31. Ausems ME, Hug CC Jr, Stanski DR, Burm AG: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. ANESTHESIOLOGY 1986; 65:362–73

32. Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. ANESTHESIOLOGY 1995; 83:8–22

33. Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs [see comments]. ANESTHESIOLOGY 1992; 76:334–41

34. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers [see comments]. ANESTHESIOLOGY 1993; 79:881–92

35. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. ANESTHESIOLOGY 1991; 74:53–63