The Safety of Target-Controlled Infusions

Thomas W. Schnider, Prof. Dr. med.,*† Charles F. Minto, MBChB, PhD, FANZCA,‡
Michel M. R. F. Struys, MD, PhD, FRCA (Hon),§‖
and Anthony R. Absalom, MBChB, FRCA, MD (UCT)§

Target-controlled infusion (TCI) technology has been available in most countries worldwide for clinical use in anesthesia for approximately 2 decades. This infusion mode uses pharmacokinetic models to calculate infusion rates necessary to reach and maintain the desired drug concentration. TCI is computationally more complex than traditional modes of drug administration. The primary difference between TCI and conventional infusions is that TCI decreases the infusion rate at regular intervals to account for the uptake of drug into saturable compartments. Although the calculated infusion rates are consistent with manually controlled infusion rates, there are concerns that TCI administration of IV anesthetics could introduce unique safety concerns. After approximately 2 decades of clinical use, it is appropriate to assess the safety of TCI. Our aim in this article was to describe safety-relevant issues related to TCI, which should have emerged after its use in millions of patients. We collected information from published medical literature, TCI manufacturers, and publicly available governmental Web sites to find evidence of safety issues with the clinical use of TCI. Although many case reports emphasize that IV anesthesia is technically more demanding than inhaled anesthesia, including human errors associated with setting up IV infusions, no data suggest that a TCI mode of drug delivery introduces unique safety issues other than selecting the wrong pharmacokinetic model. This is analogous to the risk of selecting the wrong drug with current infusion pumps. We found no evidence that TCI is not at least as safe as anesthetic administration using constant rate infusions. (Anesth Analg 2016;122:79–85)

In 1996, anesthesiologists were offered a new method of IV drug delivery, supplementing their current methods of boluses, usually given by handheld syringe, and infusions, usually administered by infusion pumps. The new option was "target-controlled infusion," or TCI, a technique intended to improve perioperative titration of IV drugs.

Because the intensity of surgical stimulation changes rapidly, titration by manually changing a constant infusion rate is suboptimal. Changes in the rate of a constant infusion do not result in sufficiently rapid changes in concentration to keep up with rapid changes in stimulus intensity. Changing infusion rates instead yields an appreciable and often undesirable lag between the new setting and the patient response. Drug concentrations are most rapidly increased by administering bolus doses and most rapidly decreased by stopping the infusion until the desired effect is achieved. This is exactly how TCI devices adjust the drug concentration, better matching the drug concentration profile to the rapidly changing intraoperative drug requirements.

From the *Department of Anesthesiology, Intensive Care, Rescue and Pain Medicine, Kantonsspital St. Gallen, Switzerland; †University of Berne, Bern, Switzerland; ‡Department of Anaesthesia, North Shore Private Hospital, Hunters Hill Private Hospital, Westmead Private Hospital, Sydney Adventist Hospital, Sydney, Australia; §Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and ‖Department of Anesthesia, Ghent University, Ghent, Belgium.

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Address correspondence to Thomas W. Schnider, Prof. Dr. med., Klinik für Anästhesiologie, Intensiv-, Rettungs-und Schmerzmedizin, Rorschacher Strasse 95, CH-9007 St.Gallen, Switzerland. Address e-mail to thomas.schnider@kssg.ch.

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Predictable recovery from drug effect is important at the end of anesthesia. On the basis of the pharmacokinetic description of an anesthetic drug, TCI can calculate an approximate time course of drug concentration after turning off the infusion, and thus provide guidance on drug administration at the end of anesthesia.

A TCI system uses the available pharmacokinetic information of the drug, that is, a pharmacokinetic model, as well as the dosing history in the individual patient to calculate the infusion rates necessary to achieve and maintain a drug concentration set by the user. For normal infusion systems (syringe pump and volumetric pump), the manufacturer's claim with regard to its performance is clearly defined and assessed as the difference between the infusion rate set by the user and the delivered infusion rate. This can be measured easily in the laboratory. One can define exactly the same relationship for a TCI system, and easily test it in a laboratory as well. Just as any specified infusion will produce a particular infusion rate with a conventional infusion pump, any given target concentration will produce a precisely reproducible profile of infusion rates over time with a TCI system. The only difference is that the infusion rate decreases at uniform intervals, as required by the pharmacokinetic model. The relationship between intended drug delivery (as determined by the TCI target concentration) and actual drug delivery is as precisely reproducible in the laboratory as the relationship between a set infusion rate and the actual delivered infusion rate. Both are determined by the device specifications and the precision and accuracy of the device engineering.

The difference between a TCI device and a conventional infusion is that a TCI device predicts the drug concentration in the plasma and (usually) at the site of drug effect. Because of the biological variability, this is never the actual

concentration. However, there is biological variability, no matter how the drug is given. The difference between the device setting (a desired drug concentration based on a pharmacokinetic model) and the actual drug concentration is relatively consistent over time with TCI drug delivery. For example, if the actual drug concentration is 10% higher than the predicted concentration after 20 minutes, then the actual concentration will very likely be 10% higher after 2 hours as well. The reason is that TCI systems are quite good at maintaining steady concentrations. With a conventional infusion, the relationship between the device setting (a desired infusion rate) and the drug concentration is not consistent over time because the concentrations will increase during constant rate infusions as the body saturates with drug. Because of their ability to maintain steady concentrations, TCI systems have less variability between what you "set" (the target drug concentration or a target infusion rate) and what you "get" (a desired drug concentration or drug effect) than conventional infusions.

Let us consider a specific example. What is the effect of 75 μg/kg/min of propofol? This question cannot be answered without knowing the dosing history for the particular patient. If 75 μg/kg/min has been given to a patient for 5 minutes, with no other drug administered, then the patient will likely be awake and conversant. However, if the patient has received propofol 200 μg/kg/min for several hours before decreasing the rate to 75 μg/kg/min, then the patient will likely be unconscious at a propofol infusion rate of 75 μg/kg/min. The reason, of course, is that it is the drug concentration, and not the drug infusion rate, that determines the drug effect. The only way to estimate the drug concentration is to know the history of drug administration in the patient. A standard infusion system knows nothing about the dosing history, and thus has no way to estimate drug concentration. A TCI system knows the infusion history, knows the extent to which the body is saturated with drug, and thus can estimate the likely concentration.

The user of a TCI system does not draw conclusions about the expected drug effect from the infusion rate, because the infusion rate does not predict drug effect. Instead, the user assesses likely drug effect from the predicted concentration. If the propofol effect-site concentration is 1 μg/mL, then the user will infer that the patient is likely sedated but conscious. If the propofol effect-site concentration is 4 μg/mL, then the user will know that it is likely that the patient is deeply unconscious. In addition, the effect-site concentrations provide insight into drug effect at the moment of observation, regardless of whether the concentrations are increasing or decreasing. This is because the effect site, by definition, is the site at which the drug concentration instantaneously produces the drug effect.

Although TCI systems have theoretical advantages compared with manually controlled infusion (MCI) systems, they must also be safe in clinical use. Albert Einstein (1879–1955) once said: "The only source of knowledge is experience." There have been approximately 2 decades of experience with TCI technology in multiple countries of the world.[1] On the basis of this, we are able to examine the real-world experience in literally millions of patients to see whether there is evidence of harm from the pharmacokinetically informed drug administration infusions provided by TCI systems in comparison with the other modes of IV anesthetic drug administration.

REPORTED RISKS

IV anesthesia, total IV anesthesia, and anesthesia using TCI are related methods of anesthetic administration. Anything that can go wrong during IV anesthesia applies also to TCI. A TCI system is an IV infusion pump, as would be used with conventional IV anesthesia, with additional software to track drug delivery using a pharmacokinetic model. The user interface is modified to enter a desired drug concentration rather than a desired infusion rate.

Potential sources of information about TCI safety issues include case reports and other types of medical publications. We searched PUBMED with the following search string ("infusion pumps/adverse effects"[MeSH Major Topic]) AND ("1995/01/01"[Date—Publication]: "2015"[Date—Publication]) OR ("target controlled infusion" AND "adverse event") OR (target-controlled infusion failure).

Formalized risk assessment is standard during the development process of new medical technology (e.g., ISO 14971). Through this process, obvious and less obvious risks of TCI will have been detected, described, and communicated to the end user. The manufacturers must report safety issues that occur after the release of a medical device to regulatory agencies.[a] These reports are publicly available. For this review, we asked several manufacturers of TCI devices to disclose this information via a survey. We also searched the Web sites of the German, Swiss, and Australian governmental organizations responsible for drug and medical device regulation.

In addition to the published medical literature and information from syringe pump manufacturers and regulatory agencies, we considered anecdotal problems related to TCI and the impact of human errors specific for the use of TCI.

PUBLISHED REPORTS

The PubMed search revealed 7 publications between 1995 and December 2014 addressing safety issues related to TCI systems.[2–8] From these 7 reports, 4 describe events that were not specific for TCI. Cox[5] reported a worn drive nut that caused a syringe pump (in this case, a TCI system) to stop drug delivery without triggering any alarm. Similar problems with Diprifusor® systems (AstraZeneca, London, UK) were described by Laurent et al.[4] Mechanical occlusion of syringe driver mechanism[9,10] is a hardware failure that is not specific to the mode of administration (MCI versus TCI). Four reports described problems with the prefilled syringes of the Diprifusor system.[1,2,6,7] These syringes are labeled with an identification tag (radio frequency), which is detected by the syringe pump. The technical problems were unrelated to the TCI mode of administration.

The only adverse event report specific to TCI appears in the Spanish Anesthesia Safety Notification System.[6] The report discusses a possible user error where the user chose the wrong pharmacokinetic model, specifically selected "propofol" for an infusion pump delivering remifentanil. With the wrong pharmacokinetic model selected, the

[a]See http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1_ol_en.pdf. Accessed July 15, 2015.

calculated infusion rates will not be appropriate, resulting in possibly significant overdose or underdose. After approximately 20 years of clinical use in millions of cases, this is the only report of a safety problem specific to TCI delivery of IV anesthetics in the medical literature.

One study investigated the safety of TCI in the magnetic resonance imaging environment.[11] The TCI device worked reliably, despite the electromagnetic radiation. Soto et al.[12] investigated the impact of cellular phones on the precision of syringe pumps. They concluded that not being able to call for help is more of a threat to a patient than the electromagnetic interference. However, it is prudent to not use a cellular phone closer than one foot from the syringe pump.[13] Some potential problems, such as the influence of electromagnetic interference on the precision of syringe pumps, are independent of the mode of IV drug administration. Other mode-independent causes of potential dosing errors include inadvertently choosing the wrong infusion rate or target concentration, mechanical obstruction of a syringe pump,[8] or choosing a nonsupported syringe.[14]

An obvious safety concern of TCI systems is the potential for errors in the calculation and control software because of memory failures. Outdated software can cause unexpected behavior. Smiths Medical reported that a syringe pump could overinfuse if the "recall last setting" function was used after an infusion in volume per time mode.[15]

A Cochrane review by Leslie et al.,[16] comprising 20 trials and 1759 patients, compared the incidence of adverse events (hypotension, apnea, movement during anesthesia) of propofol MCIs with propofol TCIs. None of the reviewed studies reported a difference. This is expected because the adverse events are dependent on the concentration of propofol, regardless of the infusion system.

Regulatory Safety Reports

These notifications about medical devices are publicly accessible via the Web sites of the regulatory agencies (e.g., for the United Kingdom: Medicines and Healthcare Products Regulatory Agency [MHRA], http://www.mhra.gov.uk). The agencies exchange information, and the same notifications can be found at different places (e.g., Swissmedic, Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM], MHRA). We found 5 notifications without recall related to TCI devices.

One report described a software error, which caused a pump to infuse 5 mL remifentanil in TCI mode. The pump then issued an error message. The report mentions a decrease of the arterial blood pressure because of this bolus injection. In another instance, the TCI system displayed an incorrect value after loading a new drug library and changes in the default pump setting. The infusion rate was correct.

The availability of "open TCI" syringe pumps has led to devices that offer more than one pharmacokinetic model. The age-adjusted propofol pharmacokinetic model for propofol developed by Schnider et al.[17,18] and the model for remifentanil developed by Minto et al.[19,20] include the calculation of lean body mass (LBM) as one of the covariates for clearance. The underlying studies for these models did not include obese subjects, and the LBM was calculated with the "James" formula. This formula predicts decreasing LBM at very high body mass indices.[21] Therefore, this formula cannot be used for LBM calculation in obese and morbidly obese patients. After the pump was available for clinical use, it was recognized that in obese and morbidly obese patients the amount administered at a given target could be different from the anesthetist's expectation. A field safety notification was issued, and the software of the TCI pump limited the use to patients with body mass index <35 kg/m^2 in women and 42 kg/m^2 in men.

Another TCI-specific field safety notification was related to the 2 implementations of the age-adjusted propofol model.[16] The pharmacokinetically savvy user of the TCI pumps recognized that the amount of propofol delivered differed during induction between 2 different implementations of the "Schnider model." TCI users were informed that they have to be aware of this difference when using different implementations of the Schnider model for propofol.

On a more educational note, one safety notification explained that the calculation of the predicted concentration is based on the assumption that no drug is administered by a route other than the TCI system. This notice addressed situations such as starting a TCI administration after the drug has been given by another infusion system or after a TCI system has been restarted.[b]

Device Manufacturer Reports

A written survey of TCI pump manufacturers (Arcomed [Regensdorf, Switzerland]; Bionet [Seoul, Republic of Korea]; Braun [Melsungen, Germany]; CareFusion [Basingstoke, UK]; Fresenius [Brésins, France]; Terumo [Tokyo, Japan]) performed by the authors also addressed safety. Specifically, we asked the manufacturers about recalls of TCI syringe pumps for safety reasons. Two companies reported that they had to recall TCI systems. In one case, the company detected a software error after releasing the pump. Only a few TCI systems were delivered at this time. Because this error could cause wrong dosing, the pumps were recalled and the software updated. No patient was harmed by the software error. In the second case, a software error caused the pump to stop infusing at low infusion rates. The pump issued an error message when it happened. This software error was related to the redundant pharmacokinetic calculations that were part of the safety features of the original "Diprifusor" system.[22] No patient was harmed by this software error.

Neither published medical literature nor information from the pump manufacturers or from the Web sites of regulatory agencies indicate safety problems related to the clinical use of TCI.

HYPOTHETICAL RISKS

Wrong Drug

Although medication errors are possible with all drugs and routes of administration, one user error that can have significant consequences during TCI use is choosing the wrong pharmacokinetic model. In the first author's institution, where >100,000 patients have received TCI anesthesia during the past 10 years, a regularly reported error is the erroneous choice of a propofol model for remifentanil TCI and/

[b]Available at: https://www.swissmedic.ch/recalllists_dl/03369/Vk_20100615_04-d1.pdf. Accessed July 21, 2015.

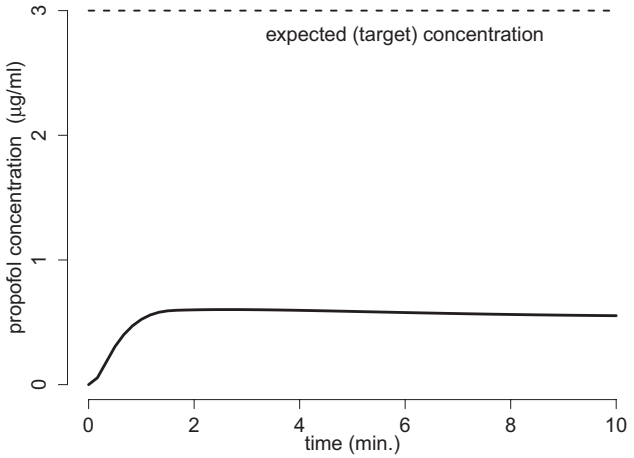

Figure 1. Simulation for confusion of pharmacokinetic model, when the remifentanil model is chosen but propofol is in the syringe. The dashed line represents the selected and expected propofol target concentration. The target-controlled infusion system calculates the required infusion rates based on a given remifentanil dilution of 50 µg/mL and a given propofol dilution of 1%, respectively. The predicted propofol concentration is much lower than the target.

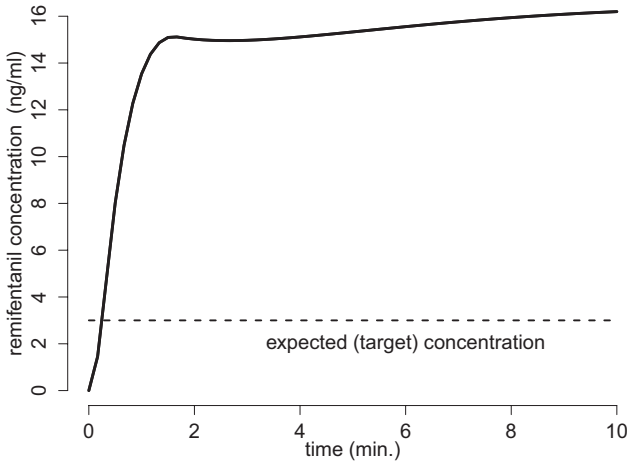

Figure 2. Simulation for confusion of pharmacokinetic model, when the propofol model is chosen but remifentanil is in the syringe. The dashed line represents the selected and expected remifentanil target concentration. With the drugs in the same dilution as in Fig 1, the remifentanil concentration peaks at a concentration of approximately 16 ng/mL. Different dilutions will result in different concentrations; the same simulation with a remifentanil concentration of 25 µg/mL will peak at a concentration of approximately 8 ng/mL.

or of the model for remifentanil for propofol TCI. This "TCI drug swap" error is analogous to the "syringe swap" error experienced by every anesthesiologist. These errors persist, despite our institutional policy regarding the setup of the TCI systems. To date, clinicians have always identified the mistake in setup before patient injury. However, similar to a syringe swap, the fact that a skilled anesthesiologist can almost mitigate the risk of injury from the swap does not preclude a substantial hypothetical risk.

We simulated the resulting drug concentrations for 2 TCI drug swap errors, one in which propofol is infused using a remifentanil pharmacokinetic model, and the converse where remifentanil is infused using on a propofol pharmacokinetic model. Our simulations assumed swapping the pharmacokinetic model of Schnider et al.[17,18] with a k_{e0} of 0.456/min for propofol and the model of Minto et al.[19,20] for remifentanil. Our simulations assumed that propofol 1% and remifentanil 50 µg/mL are the 2 drugs intended to be given as TCI to a man, age 40 years, weight 70 kg, height 1.7 m. We also assumed that the anesthesiologist intended to administer a target effect-site concentration of 3 µg/mL of propofol (first simulation) and 3 ng/mL of remifentanil (second simulation).

Figure 1 shows the resulting propofol concentrations when the user has mistakenly selected remifentanil. The pump calculates the necessary volume, based on a supposition that it is giving remifentanil in a dilution of 50 µg/mL. It begins with an initial bolus of just 1 mL, obviously much lower than necessary! The drug concentrations remain approximately 0.6 µg/mL, well below the desired propofol concentration of 3 µg/mL.

Figure 2 shows the resulting remifentanil concentrations when the propofol model has mistakenly been selected. The result is a peak remifentanil concentration of approximately 16 ng/mL, well over the desired target of 3 ng/mL.

When remifentanil and propofol are used together for anesthesia, there is the possibility for both syringe pumps to be swapped (Fig. 3). The patient would receive a low

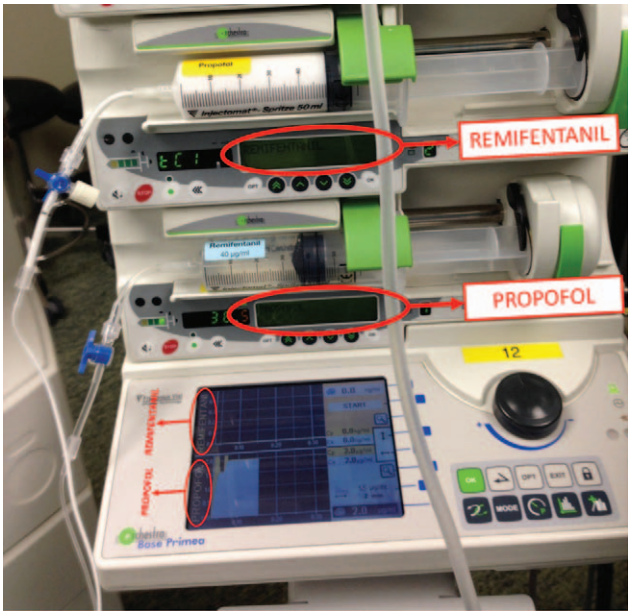

Figure 3. Drug swap (real example): The displays of the syringe pumps and the display of the base system indicate the drug swap. A propofol target concentration of "2" has been selected but the pump delivered remifentanil because of the syringe swap.

concentration of propofol and a very high concentration of remifentanil. The remifentanil concentration is sufficiently high to cause thoracic rigidity.

The "5 rights" of drug administration should prevent this: right drug, right dose, right route, right time, and right patient. Although most TCI systems have confirmation steps for verification of the drug and pharmacokinetic model, in the authors' experience this does not prevent TCI drug swap errors. Automatic detection of the drug by the pump through a labeled syringe as implemented in the Diprifusor system does prevent this error. However,

because the Diprifusor only administers propofol, avoidance of TCI drug swaps was mostly a matter of fundamental limitation of the device to propofol, a limitation no longer accepted after the introduction of second-generation TCI systems that offer a choice of drugs. Nevertheless, although TCI drug swaps happen, there is neither any published evidence of injury from such a swap nor is there any reason to think that drug swaps with TCI are more likely than drug swaps with conventional infusion pumps.

Intersubject Variability

Pharmacokinetic models are valid for the population from which they are derived. Extrapolation to other populations has limitations. This limitation applies to all forms of drug dosing, whether conventional boluses and infusions or dosing using TCI. Therefore, choosing the appropriate dose and infusion rate for a conventional total IV anesthesia has the same uncertainty as choosing the appropriate target concentration.

The accuracy and safety of conventional infusion pumps are evaluated by whether the pump delivers the amount of drug per time that the user has set. Because of pharmacokinetic variability, the concentrations will be different among different patients. The same standard should apply to TCI systems. When the user selects a target concentration, a time course of drug delivery is established, consisting of the initial bolus followed by an exponentially declining infusion. Exactly like giving a bolus of drug from a syringe, or administering an infusion with a conventional infusion pump, a TCI system will always calculate exactly the same infusion rates over time for patients with the same covariates for a given target concentration. The accuracy of the TCI device should be evaluated exactly as the accuracy of a conventional infusion device is assessed: does the device precisely follow the dosing profile specified by the target concentration, the pharmacokinetic model, and the patient covariates? This can be assessed at a laboratory bench, exactly as it is assessed for a conventional infusion pump.

Pharmacokinetic variability is a biological fact. It is not a "bug" in the pharmacokinetic model or TCI software. Pharmacokinetic variability exists no matter how drugs are given. On the basis of linear systems theory, it can be mathematically proven that intersubject variability in concentration is necessarily less with TCI than with bolus drug delivery.[22] If drugs are approved for bolus drug delivery, for example, propofol and remifentanil, then any argument that TCI infusion systems should not be approved because of intersubject variability in observed drug concentrations is demonstrably false. TCI systems demonstrably reduce variability by (1) incorporating known pharmacokinetic covariates into models too complex to address with manual infusions, and (2) eliminating much of the time-varying variability. With conventional infusions, the ratio between infusion rate and plasma drug concentration dramatically changes over time and with infusion history. With TCI, the ratio between target drug concentration and actual drug in the plasma or at the effect-site concentration shows far less variability, being relatively insensitive to both time and infusion history. TCI has the potential to support safe dosing by making titration to effect simpler.

Regulatory Implications

After the successful introduction of TCI in Europe, an effort to have TCI approved in the United States was unsuccessful. We suggest that the fundamental reason relates to the nature of the claim made for a TCI device. If a company makes a claim that "our TCI device targets and maintains a plasma concentration" of a certain drug, we expect the Food and Drug Administration (FDA) to evaluate this claim examining whether the concentrations in the patient match the setting on the pump. Such a claim forces the FDA to hold the TCI device accountable for subject-to-subject pharmacokinetic variability, an unrealistic expectation. Given that TCI devices do not magically eliminate intersubject variability, it is not surprising that no TCI device has been approved by the FDA.

Therefore, from a regulatory perspective, the claim (with regard to safety and accuracy) of a TCI system should be that with a given setting (i.e., target concentration) the TCI device will deliver a defined infusion profile based on the selected pharmacokinetic model and specific patient characteristics. The infusion profile can be verified mathematically. The accuracy of achieving the profile can be verified on the laboratory bench. The justification for the profile is that the drug concentrations in the plasma or at the site of drug effect are more stable over time than with other forms of IV drug administration, and hence clinically desirable.

DISCUSSION

TCI was commercially launched at the 1996 World Congress of Anaesthesiologists in Sydney, Australia. Anesthesiologists had to learn a new dosing paradigm. In anesthesia, perhaps more than in other medical specialties, drug is titrated to effect. Fortunately, TCI administration of IV anesthetics leverages the training that anesthesiologists have in titration of volatile anesthetics. Most anesthesiologists have no idea of the actual dose of volatile anesthetic delivered to a patient. Instead, they set a concentration (partial pressure) on a vaporizer. This is the steady-state partial pressure to which the patient's lungs, blood, and brain eventually equilibrate. For anesthesiologists, concentration-based dosing is intuitive.[23] This likely explains the finding that educated anesthesiologists would prefer to use TCI to conventional infusions if the devices were available.[24]

There are theoretical and practical advantages of using TCI. Neither the medical literature nor other sources of information suggest that TCI administration of drugs is less safe than administration by constant MCI rates.

Some of the reported errors with syringe pumps are human errors[25] that could be prevented by careful teaching of the correct use and the limitations of the device.[26] The human errors are also amenable to improved device design. A future generation of TCI devices may introduce additional checks on input, monitor whether the effect-site concentration is within the desired therapeutic window, and trigger alarms if the chosen infusion scheme is inappropriate. They could even incorporate scanners to reduce the possibility of TCI drug swaps. TCI pumps have the potential to reduce medication errors,[c] provided users receive adequate training.[27] On the basis of the published medical literature, TCI is

[c]Available at: http://www.apsf.org/newsletters/html/2003/spring/smartpump.htm. Accessed July 15, 2015.

at least as safe as the alternative delivery mode of constant rate infusions.

Like all medical devices, syringe pumps fail occasionally. These failures are unrelated to the mode of administration. The few available reports of pump failures suggest that they most commonly occur when the pump is providing conventional constant rate infusions. This does not mean that constant rate infusions are more likely to be associated with pump failures but rather that the TCI mode does not appear to predispose to pump failure.

TCI systems work reliably when exposed to strong electromagnetic signals.[10] This is not surprising because there is nothing magically vulnerable about the TCI software in these devices. All modern syringe pumps have microprocessors running computer programs that control drug administration. As a result, all pumps should be equally vulnerable, or equally resistant, to external interference from electromagnetic exposure.

The choice of the pharmacokinetic model for a TCI-delivered drug affects the amount of drug administered over time. Different implementations of published pharmacokinetic models for propofol have resulted in safety notifications.[d] Because both implementations referred to the same publication, most users were not aware that the pumps would deliver different amounts of propofol for the initial minutes after a concentration was selected. Despite this discrepancy, no patient harm has been reported. In our view, this represents the type of divergence that happens when investigators and companies "go it alone" without central guidance. The solution is harmonization of pharmacokinetic algorithms and parameters for TCI drug delivery. The "Open TCI Initiative" is a worldwide collaboration among interested investigators, clinicians, and medical device companies to create standards for TCI.[e] TCI approval by the FDA would provide additional guidance to harmonize TCI implementations worldwide.

For this article, we used different sources of information. We used a comprehensive search strategy to avoid missing publications. However, we cannot be confident that we identified every relevant report. Not all the TCI manufacturers replied to our survey. It is possible that safety issues remain hidden by the nonresponding medical device companies. However, the companies who responded to our survey have a significant market share of all the installed TCI systems. We also accessed the publicly available information from the Web sites of the regulatory agencies. Finally, the authors are from 3 countries in which TCI is routinely used. We cannot exclude the possibility that our review failed to identify a significant safety concern. However, the lack of a theoretical basis for unique safety concerns, combined with congruent findings from literature searches, company questionnaires, and regulatory data suggest that there is no significant safety concern with TCI systems.

Twenty years of worldwide clinical experience with TCI has produced only 7 reports of medication (TCI drug swaps) and technical errors (related to the syringe pump). Not one of the reports was clinically consequential. Not a single report has identified an adverse incident that was related to the TCI algorithm for a pharmacokinetically based infusion. If we conservatively and very roughly estimate that 20,000 TCI systems are used worldwide, are used approximately 200 times per year, and have been used for 5 years, then a very approximate denominator for the incidence of adverse events is 20 million TCI users. Because there have been no reported adverse events in 20,000,000 users, by the "rule of 3" the upper 95% confidence boundary on the risk of a series adverse event is <1:7 million.[28]

[d]Available at: http://www.hfs.scot.nhs.uk/publications/PSAN0801.pdf. Accessed July 21, 2015.

[e]Available at: http://www.opentci.org. Accessed July 15, 2015.

DISCLOSURES

Name: Thomas W. Schnider, Prof. Dr. med.
Contribution: This author attests to the integrity of the original data and also wrote the manuscript.
Attestation: Thomas W. Schnider approved the final manuscript.
Conflicts of Interest: Thomas W. Schnider is a paid consultant for Codan Medical (Switzerland).
Name: Charles F. Minto, MBChB, PhD, FANZCA.
Contribution: This author attests to the integrity of the original data and also helped write the manuscript.
Attestation: Charles F. Minto approved the final manuscript.
Conflicts of Interest: Charles F. Minto is a paid consultant for Codan Medical (Switzerland).
Name: Michel M. R. F. Struys, MD, PhD, FRCA (Hon).
Contribution: This author attests to the integrity of the original data and also helped write the manuscript.
Attestation: Michel M. R. F. Struys approved the final manuscript.
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Name: Anthony R. Absalom, MBChB, FRCA, MD (UCT).
Contribution: Anthony R. Absalom attests the integrity of the original data and also helped write the manuscript.
Attestation: Anthony R. Absalom approved the final manuscript.
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This manuscript was handled by: Steven L. Shafer, MD.

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