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Tips and Tricks to optimize Total Intravenous Anesthesia

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Key Points

To err is human. Guidelines and Standard Operating Procedures (SOPs) can help reduce mistakes during Total Intravenous Anesthesia (TIVA). When using infusion pumps, it is essential that clinical staff know how to use them, and their limitations. Safe and effective management of continuous drug infusions depends on the understanding of the dynamics of the delivery system :

- Clear labelling of intravenous syringes, connectors and valves is mandatory. Color coding or bar code checks are recommended.
- Too high drug concentrations in syringes with correspondingly low infusion rates should be avoided. The higher the concentration, the higher the physical error of administration.
- Sites of intravenous infusions should ideally be visible at all time, so that they can be monitored for disconnection, leaks or subcutaneous tissuing. If not visible, safe and unobstructed connections are recommended.
- A non-return valve should be used on any intravenous fluid line, ideally with anti-syphoning for gravity infusions.
- The dead space volume of fluid between the point at which infusions are combined and the IV cannula should be minimized.
- Carrier flow rate should not vary a lot and intravenous anesthetic agents are best placed as proximal as possible to the IV access.
- Knowledge of the particularities of the pharmacokinetic model implemented in the TCI system is crucial, as well as the typical recommended plasma and effect site concentrations according to the type of patient, type of surgery, and anesthesia phase.

Introduction

Propofol-based Total Intravenous Anesthesia (TIVA) has a number of important advantages over volatile techniques. Intravenous drugs can be used for anxiolysis and/or sedation, cause less pollution, and allow free airway access. In addition, propofol markedly decreases the risk of postoperative nausea and vomiting (PONV), and does not induce malignant hyperthermia (1). There are also several well documented advantages with regards to free radical scavenging, as well as immune and organ function (1).

Target-Controlled Infusion (TCI) is a method for administering TIVA, which is analogous to a calibrated vaporizer for volatile anesthetics. A computer system controls an infusion device, which is pre-programmed with pharmacokinetic data derived from a patient population. The user enters individual physical characteristics of the patient (the covariates, such as demographic parameters like weight, height, age, and gender) into the TCI system, which then allows it generating and maintaining calculated and predicted blood and effect site concentrations (Ce). Unfortunately, unlike vaporizers, the syringe pumps and TCI systems are currently still not integrated into the anesthesia machine. Moreover, vaporizers are designed to be specific for one volatile agent. Volatile drug concentrations can also be easily measured in the circuit.

Since 2000 (2), no article emphasizing on the scientific basis of the optimized clinical practice of TIVA can be found in the literature. The purpose of this review is to share the experience and expertise of different centers and anesthesiologists from several countries, and propose some practical guide-

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lines to optimize the practice of TIVA with regards to drug preparation, delivery, and titration with TCI.

Drug preparation

Preparation and storage of IV anesthetic medications according to proper hygienic protocols is mandatory and fundamental to safe TIVA. Most IV anesthetic agents are available at various concentrations. Multiple drawings for different patients from the same vial must be avoided, and all recommendations of the manufacturer have to be followed. The concentration of propofol (0.5%, 1% or 2%), and the dilution of opioids such as remifentanil (100, 50, 40, 20 or 10 μg/mL) and sufentanil must always be checked. Up to now, there is no published chemical interaction between remifentanil, propofol and most regularly used muscle relaxants.

When using volatile anesthetic agents, the risk of labelling error is small. With the exception of Diprifusor™ pre-filled syringes, generic drug TIVA is at much higher risk of labelling errors, and, therefore, special attention should be paid to insure proper identification. Some institutions have introduced a double-checking policy on drug labelling before use, and standardize the setup of drug dilution, make of syringe, and pump setup for the whole anesthesia department. Written protocols for preparing the different IV anesthetic drugs are helpful when there is frequent turnover of anesthetic staff, and may reduce administration errors. The best choice in that respect may be to reduce the number of TIVA and TCI options of the pumps. An institutional clear standard operating procedure (SOP) for setting up the pumps, with only one pharmacokinetic model option, and only one dilution/concentration for each IV anesthetic drug is the safest.

Drug delivery

1) *Infusion devices*

Most infusion devices have a flow rate accuracy of ± 5%, meaning that, over the complete period of infusion, the flow rate (in mL/hour) will not vary beyond these limits. In that respect, syringe drivers outperform volumetric pumps, particularly when small volumes are delivered. The manufacturers define the accuracy of the linear displacement of the plunger. This is the mechanical accuracy of the pump itself, which excludes the additional error caused by the inconsistency of single-use syringes. This may cause additional flow deviations of up to 4% greater than those specified for the infusion device (3).

The physical performance error of commercial syringe pumps incorporating the Diprifusor™ module to deliver propofol through a target-controlled infusion has been tested in a laboratory experiment (4). Despite between pumps differences, which may be related to the synchronization of the hardware components, the absolute inaccuracies in physical performance are low and, presumably, negligible from a clinical perspective.

Moreover, the anesthesiologist should always be aware of the trumpet curve phenomenon of an infusion device. This means that the error between the displayed and real pump infusion rate is maximal at the start of the infusion (Fig. 1). When plotting the dose error of a given medication over time at a fixed infusion rate, the obtained curve looks like a trumpet, converging to the right side. The upper and the lower curves correspond to the maximum positive and negative percentage deviation from the expected dose given by the pump, relative to the time duration of infusion. This trumpet behavior could be relevant in clinical practice, especially when the initial drug infusion rate is slow, or the volume of the initial loading bolus is small.

Before induction, the plunger of the syringe pump must be properly engaged, in order to be sure that, when the TCI is starting, the drug is effectively given. Checking for adequate position of the plunger is particularly of importance when the anesthetic drug is highly concentrated, or when the initial target concentration is very low. Indeed, in those cases, the initial loading dose is small, which yields to small infusion volumes. When changing syringes, the plunger must also be correctly pushed. Very short acting medications such as remifentanil must be prepared in advance, so that no delay occurs at the time of syringe replacement. When replacing the syringe and restarting the infusion, the infusion device procedure check must be carefully followed.

When using infusion equipment, clinical staff members must formally be trained to its use, and have a comprehensive introduction to the operations of the devices, in order to thoroughly familiarize with them. The national and local requirements for medical devices apply (3, 5). Pump pressure monitoring is mandatory, and can warn of a disconnection or obstruction of the IV line.

Infusion pumps are mechanical devices, with potential mechanical flaws that may affect the accuracy. Therefore, a good maintenance plan is

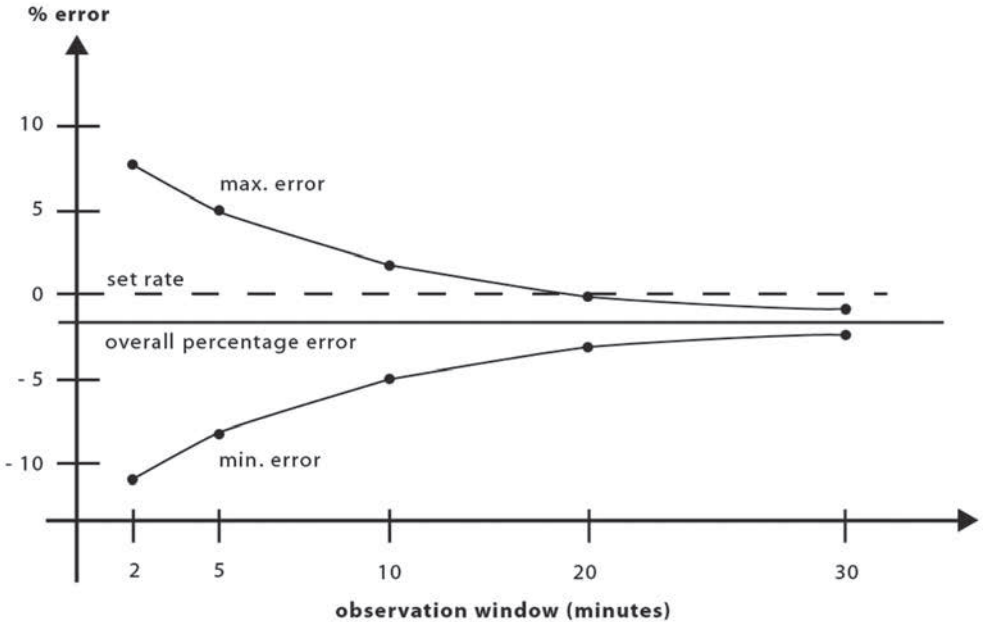

Fig. 1. — Evolution of the dose error over time when a drug is given at a fixed infusion rate. The shape of the curve looks like a trumpet converging to the right side. The units on the x axis are time in minutes. The y axis corresponds to the percentage of the dose error. The upper and the lower curves correspond to the maximum positive and negative percentage deviation from the expected dose given by the pump, relative to the time duration of infusion.

mandatory to guarantee operation within the specifications of the manufacturer.

2) *Infusion lines*

To avoid air or leaks along the infusion lines, all connections must be Luer lock. These connections must be tightly locked, although not so tight as to risk a crack. This can also be associated with a drug leak. Leakage along an infusion line exposes to the risk of inadequate level of anesthesia. A drug leak is more dangerous with remifentanil, because of its very short duration of action. A leak of propofol is more visible, due to its white color. The tube compliance is also important. A closed one meter standard IV line under pressure is able to accumulate several milliliters of fluid. Additionally, compressible air in the syringe has a major impact on the onset time of the pressure alarm trigger, in case of a line interruption. Fluids are not compressible, in contrast to air and plastics.

Accidental occlusions of the IV line, due to improper positioning of stopcocks or clamps, and kinked tubing, must be avoided. Occlusions between the pump and the patient alter the ability of maintaining stable plasma drug concentration. Until occlusion is detected, the pump will infuse, raising pressure in the delivery set. When the occlusion is released, the built up pressure will lead to an uncontrolled bolus. The bolus magnitude after releasing an occlusion is highly dependent on the amount of air in the system, and on the stiffness of the tubing system. With concentrated anesthetic medications, this bolus can produce a large perturbation in the patient physiological status, and may lead to hemodynamic instability (3). Figure 2 illustrates remifentanil Ce profile when a 20 or 50 μg bolus is inadvertently administered in a 40 year old 70 kg male patient, and after a 1 hour infusion at 0.2 μg/kg/hour. The 20 μg bolus increases Ce from 5.3 to 6.5 ng/mL, whereas the 50 μg bolus increases Ce from 5.3 to 8 ng/mL. More complex situations can occur in case of incomplete occlusion, and, for example, position-dependent resistance variations in the infusion line. Consequently, the presence of air in the syringe may lead to irregular infusion rates and, hence, instability, as well as delays in the onset of the occlusion alarm and air embolism.

The dynamics of intravenous drug delivery resulting from drug infusions connected and mixed to maintenance fluids can be complex. It depends on the infusion rate, carrier flow rate, and dead space volume between the point where infusion lines are connected and the IV cannula (5, 6). In case of a need for an extension of lines to keep access to the stopcocks, each pump line should ideally be extended individually, in addition to the insertion of a free stopcock on the main IV line, rather than extending the main IV line only.

The anesthesiologist must also ideally try to avoid any interruption of the IV infusion, such as by a non-invasive blood pressure cuff, a tourniquet, or

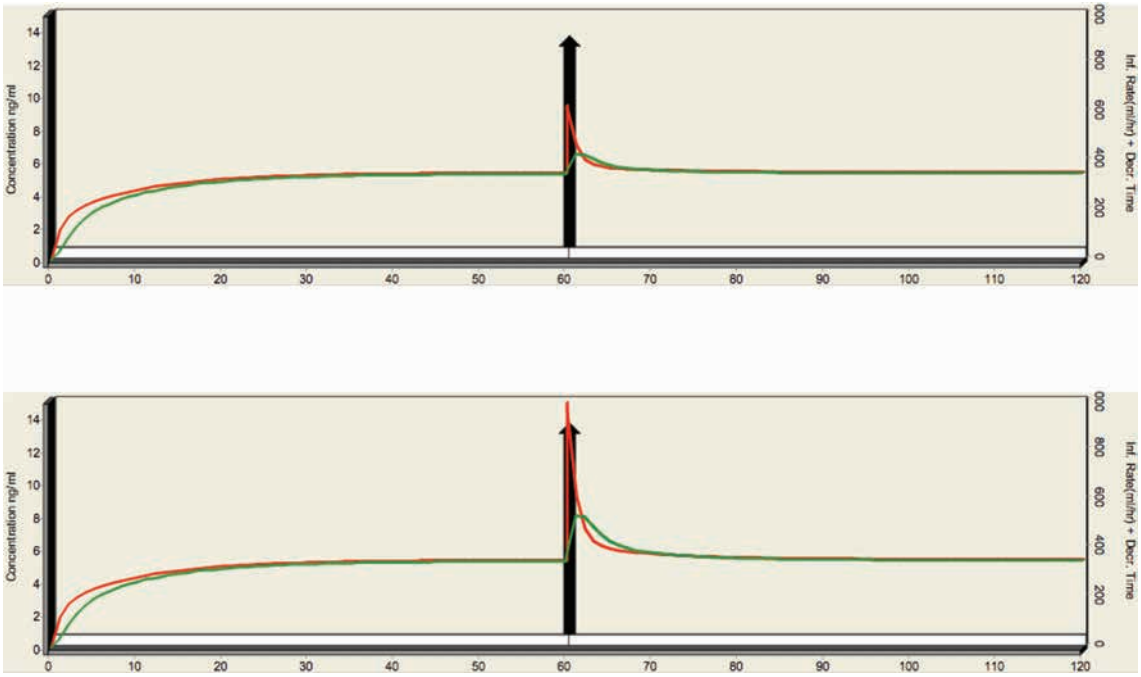

Fig. 2. — Pharmacokinetic simulation of a bolus injection of either 20 or 50 μg of remifentanil after 1 hour infusion of remifentanil at 0.2 μg/kg/hour, in a 40 yr old male patient, weighing 70 kg. The bolus of 20 μg increases remifentanil Ce from 5.3 ng/mL to 6.5 ng/mL, whereas the bolus of 50 μg increases it from 5.3 to 8 ng/mL (TIVA Trainer software, www.eurosiva.eu).

the surgical procedure itself (e.g. during shoulder surgery). The site of the intravenous cannula should ideally be accessible at all times.

3) *Dead space*

Although the concept of dead space is intuitive, ignoring its interaction with the carrier and drug flow rates can lead to unintended clinical effects. These effects will result from large variations in the delivery rate of potent IV anesthetic drugs (5, 6, 7). In clinical settings, the carrier flow rate may become transiently interrupted or modified, such as during the replacement of an empty fluid bag, or after a change in the height of the pole on which the bag is placed (Fig. 3).

Mathematical models have been built to quantify these interactions (7, 8). The models predict a lag in response time to changes in carrier or drug flow, which is proportional to the dead space and inversely related to the total flow rate. Increasing the carrier rate provides an acute drug bolus. Temporary reduction or cessation of carrier flow decreases the rate of drug delivery, potentially for prolonged periods. In addition, a drug bolus occurs at restoration of the carrier flow. Therefore, although complex, the impact of infusion set architecture and changes in carrier and drug flow rates are predictable. The anesthesiologist must always keep the dead space and the carrier flow rate in mind to optimize and guarantee the safe use of IV drug infusion.

Figure 3 shows the complex behavior of a classic plasma propofol TCI, using the pharmacokinetic set of Marsh, combined with a 0.25 μg/kg/min manual continuous infusion of remifentanil in a patient weighing 67 kg. Using a high remifentanil drug dilution of 0.1 mg/mL, remifentanil is infused at the low flow rate of 10 mL/hour. The dead space volume between entrance of both IV anesthetic drugs and the final point of venous entry is 1 mL. After 180 minutes of continuous stable propofol plasma TCI, targeted at 4 μg/mL, a decrease in propofol target from 4 to 2 μg/mL will stop the TCI system for 8 minutes. This will also decrease the amount of remifentanil delivered to the patient, insofar as propofol acts as a carrier for the remifentanil infusion. Propofol and remifentanil also act synergistically. Changing the ratio between propofol and remifentanil concentration will also change the theoretical propofol concentration at which 50% of the patients will wake up (TIVA Trainer software, www.eurosiva.eu).

Noteworthy, in Figure 3, remifentanil concentration is halved for a short period of time following the decrease in propofol infusion-related carrier flow rate. According to remifentanil and propofol synergy, the net effect on propofol pharmacodynamics is larger than intended. The use of very low

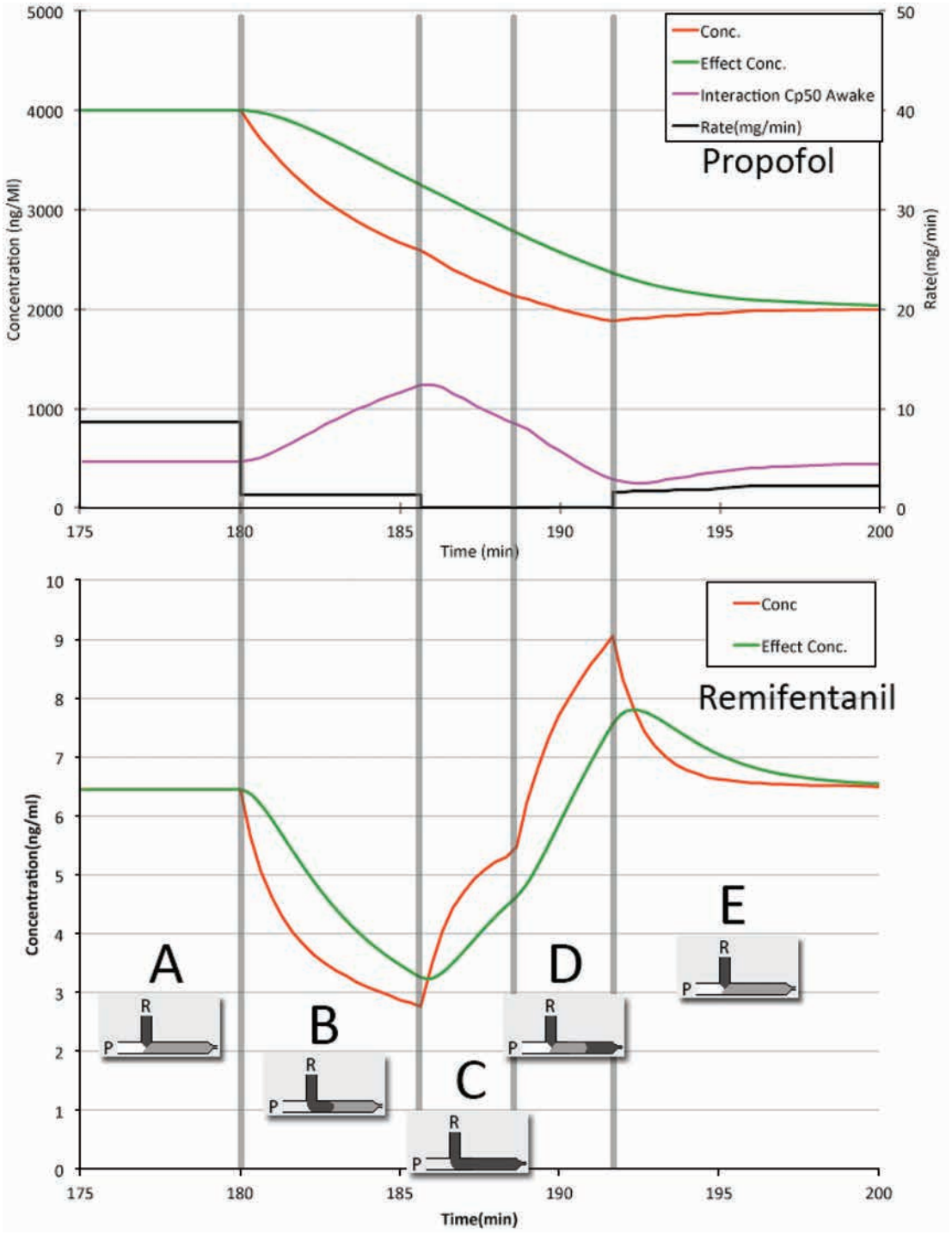

Fig. 3. — TIVA Trainer simulation (www.eurosiva.eu) of the effect of dead space when propofol 1% is given to a 67 kg patient using the Marsh model for plasma TCI at a target of 4 μg/mL, and combined with remifentanil at 0.25 μg/kg/min (flow rate of 10 mL/hour of a 0.1 mg/mL remifentanil solution). Remifentanil is connected to the same line and the volume of the infusion line holding the combination of both drugs is 1 mL. The target of propofol is decreased after 180 minutes from 4 to 2 μg/mL. The propofol infusion stops for 8 minutes and then resumes. This influences the remifentanil delivery because propofol also acts as a carrier. The process in the dead space volume of 1 mL can be divided into several consecutive stages :

A. Both infusion running and a mixture of propofol and remifentanil enters the vein.

B. Propofol infusion stops and the mixture of phase A is pushed out by the remifentanil infusion alone. The amount of delivered remifentanil is therefore lower than intended, and the concentration drops. Propofol is still running into the vein because it is part of the mixture contained in the dead space (black line). Taking account of remifentanil and propofol interactions, the expected propofol concentration at which 50% of the patients will be awake also increases (purple line).

C. The remifentanil infusion has passed the dead space and the delivered amount of remifentanil equals the amount that leaves the infusion pump. This will cause the remifentanil Ce to increase.

D. Propofol starts running again and pushes out concentrated remifentanil. This will cause an overshoot in remifentanil concentration.

E. The propofol-remifentanil mixture is running into the patient and intended blood concentrations are restored.

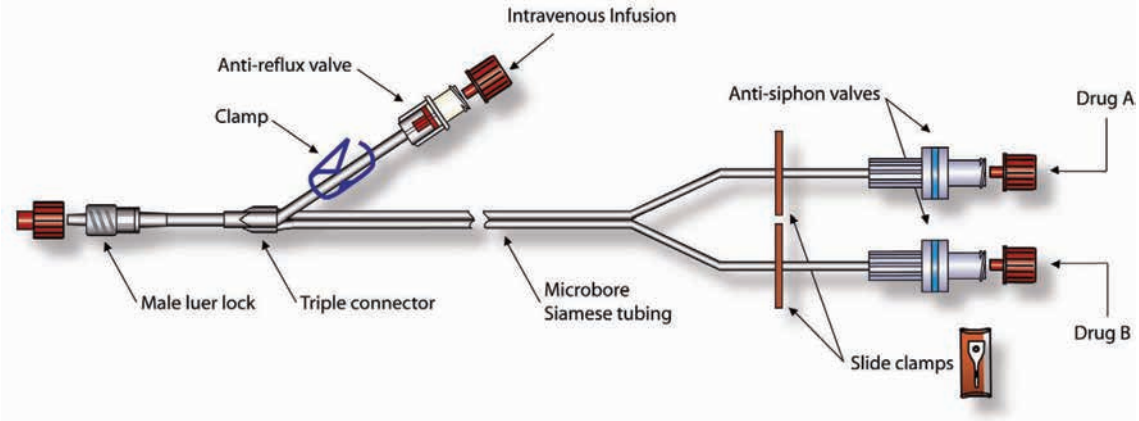

Fig. 4. — Typical arrangement of a multi-lumen connector including an anti-reflux valve for IV fluid and anti-siphon valves for IV drugs.

dead space volume prevents those disturbances. High drug concentration such as 0.1 mg/mL remifentanil is associated with very low infusion rates. Consequently, changes in remifentanil plasma and effect site concentrations after interrupting and restarting the carrier flow are larger than those observed with higher remifentanil dilution and rates (e.g. 0.02 mg/mL). Figure 3 nicely illustrates the effect of different remifentanil concentrations during a propofol-remifentanil TCI on depth of anesthesia. It shows that it can be associated with a high risk of awakening (purple line = concentration with a 50% probability of awakening = C_{50}).

When using multiple access ports on IV lines, the dead space can significantly affect drug delivery dynamics during continuous infusions. Some studies provide quantitative support for the concept that the most critical infusion should join the system at the patient closest port (9). Ideally, TIVA drugs should be directly connected to a dedicated IV line. If the TIVA drugs are administered alongside a gravity infusion, they must be placed as proximal as possible to the IV access, and protected from the main gravity infusion by a one way/anti-reflux valve. This is the opinion and the clinical practice of the experienced TIVA anesthesiologists who already have seen a propofol reflux into the main infusion line. There exist specifically designed infusion sets for that purpose (Fig. 4). Multi-infusion therapy through central venous lines is common in the Intensive Care Unit (ICU), or during TIVA for complex surgery. Again, a dedicated IV line for anesthetic agents avoids major perturbation in drug delivery (6). For TIVA, particularly when using TCI, a combination of an opioid, propofol and neuromuscular blocking drug infusion necessitates ideally a 3-way tap with one-way valves at each port (Fig. 5).

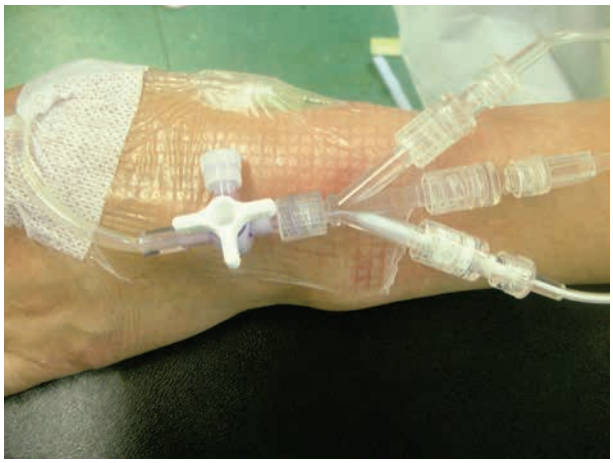

Fig. 5. — Arrangement of three anti-reflux valves for propofol and remifentanil TCI that are pushed by the carrier flow placed in the middle. The dead space is one mL.

In clinical practice, the dead space should be reduced as much as possible. As exposed above, it greatly influences the stability of drug delivery, particularly at low infusion rates. When an infusion is designed to give a flow rate of less than 2 mL/h, using a 50 mL syringe, a lesser concentration should be considered. Flushing the IV cannula at the end of the case after all infusions have stopped is recommended, particularly in children, where residual anesthetic drug inside the cannula or IV line can expose to unintentional dead space flushing, either in the recovery room or on the ward.

TCI PROGRAMMING

Although several pharmacokinetic models can be found in the literature, only two pharmacokinetic sets for propofol (10, 11) and only one pharmacokinetic set for remifentanil (12) and sufentanil (13)

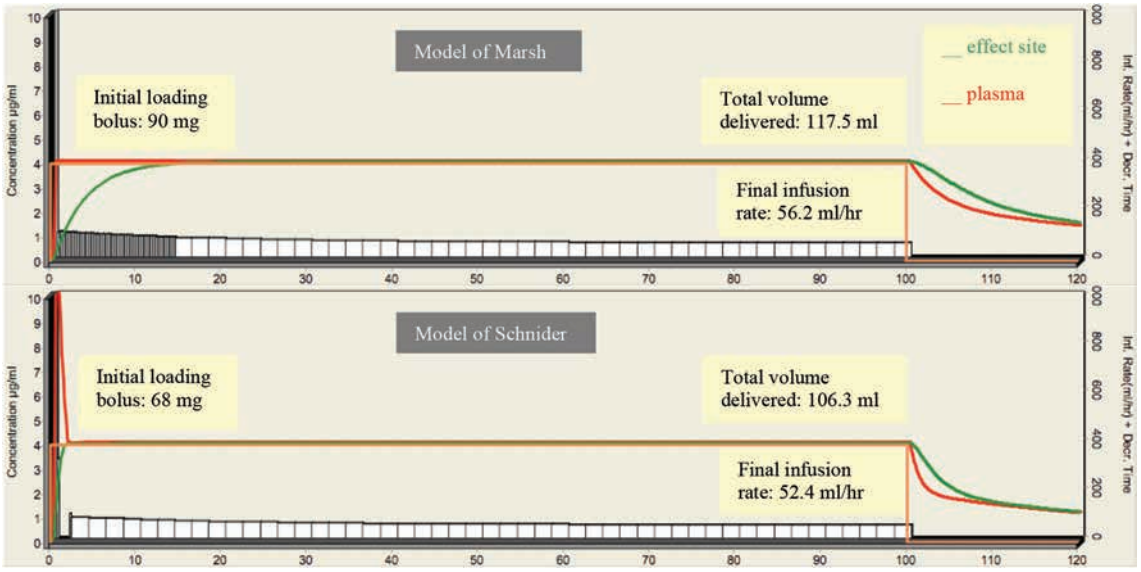

Fig. 6. — Pharmacokinetic simulation of a plasma TCI of propofol targeted at 4 μg/ml in a 40 yr old male patient weighting 70 kg, using the set of Marsh (upper graph) or the set of Schnider (lower graph). It nicely illustrates the differences between both propofol pharmacokinetic sets. The initial loading dose of propofol is 90 and 68 mg with the sets of Marsh and Schnider, respectively. After 100 minutes, the total infused volume is 117.5 and 106.3 mL and the final infusion rates are 56.2 and 52.4 mL/hour, for the sets of Marsh and Schnider, respectively.

have been implemented into the commercial TCI pumps. All these pharmacokinetic sets have been validated by other teams, and have been demonstrated to be associated with an acceptable predictive accuracy and bias in an adult population of healthy patients (14).

Provided that an adequate model is chosen, effect-site targeting is possible with all available TCI devices for generic propofol. The only exception is the Diprifusor™ , which allows plasma targeting only, while calculating and displaying the effect site concentration. The Diprifusor™ can only be used with a glass prefilled syringe of Diprivan® that uses a special electronic tag for drug recognition.

Although modern infusion pumps can be set to detect low or high pressure, there is no disconnection alarm for TCI anesthesia. Moreover, TCI calculated plasma concentrations of intravenous anesthetic drugs cannot be measured *in vivo*. This contrasts with the ability of continuously measuring volatile anesthetic agent end-tidal concentration. Such measurement guarantees that the anesthetic agent is delivered and present in the body. To decrease the risk of awareness and recall, it is recommended to avoid or minimize the use of muscle relaxants. The reason is that movement constitutes an "early" warning of rising consciousness or pain. Objective EEG-based monitoring of the depth of the hypnotic component of anesthesia should always be considered when a patient is fully paralyzed. Such monitoring is also valuable in ASA 4 and 5, obese and elderly patients, or during very long surgical procedures.

1) *What is the most appropriate propofol pharmacokinetic data set ?*

The set of Marsh is derived from venous sampling and was designed for plasma control (10). Pharmacodynamic measurements were not made in the original study, and a theoretical effect-site compartment constant (Ke0) of 0.26 min^{-1} was added to the model. This constant was based on the analysis of the hysteresis between blood concentration and effect as measured by auditory evoked responses. This was done in a group of male patients, and presented as a poster during the World Congress of Anesthesiologists in Sydney, Australia. In the Marsh model, the central compartment (V1) is large and all covariates are fixed. A recent refinement of the model has been introduced, and uses covariates that take account of clearance and central compartment size in older patients (15). The set of Schnider should preferably be used in the "effect" control mode (11). When selecting the same initial target value, the set of Marsh for blood control will initially administer more propofol than the Schnider set. The main reason for this is the larger volume of the central compartment in the Marsh model. In clinical practice, a higher propofol Ce is often required to achieve loss of consciousness when using

the Schnider set, as compared to the plasma concentration required when using the Marsh model. However, the clearance of both models is similar and, consequently, the delivery rates to maintain stable propofol concentrations at steady state are similar.

A pharmacokinetic simulation can demonstrate the differences between both techniques. In Figure 6, a plasma TCI using the set of Marsh, and an effect-site TCI of propofol 1% using the set of Schnider, both targeted at 4 μg/mL in a 40 yr old male patient weighting 70 kg are shown. It nicely illustrates the differences between both propofol TCI techniques. The initial loading dose of propofol is 90 and 68 mg with the sets of Marsh and Schnider, respectively. After 100 minutes, the total infused volume is 117.5 and 106.3 mL, and the final infusion rates are 56.2 and 52.4 mL/hour, for the sets of Marsh and Schnider, respectively.

Both pharmacokinetic sets can be used and selected in adult patients, but not in children. In the obese patients, the prospective validation of either model is lacking. Therefore, in patients with a body mass index higher than 30, propofol TCI should be very carefully clinically monitored. Deviations from the model predictions can be significant. Recently, Ingrande et al. have suggested that the lean body weight is a more appropriate weight-based scalar for propofol infusion during induction of general anesthesia in moderately obese subjects than the total body weight (16).

Both models produce stable blood concentrations that can be up and down adjusted according to individual patient requirements. Common sense recommends that individual anesthesiologists preferably use the one they are most familiar with. It may even be advisable to decide on one specific model for a given department, and make it the standard. This may avoid confusion or mistakes when switching between models.

One of the clinically perceived disadvantages of TCI is the required time to enter the patient parameters and confirming pump settings. With some systems, this is required for each drug. However, this must not preclude resetting the system entirely when a new patient is connected, even if patient data are the same.

2) *What is the best target for propofol ?*

Propofol EC 50/95 is the effective concentration that will prevent reflex movement in response to surgical incision in 50 or 95 % of patients. This concept is similar to the minimal anesthetic agent concentration (MAC) of the inhaled anesthetic agents. EC 50/95 is reduced when nitrous oxide, a benzodiazepine, an alpha-2 agonist or an opioid is added (17). It is a population-based statistical concept. Hence, it is very important to keep in mind that inter-individual variability in propofol requirement is large. Consequently, titration to individual effect is essential. For induction in healthy non-premedicated ASA 1 or 2 adult patients, a propofol concentration of 4 to 6 μg/mL is most often needed. In premedicated or co-induced patients receiving concomitantly a benzodiazepine, another sedative agent or an opioid, an alternative consists in setting an initial effect-site propofol target concentration between 2 and 3 μg/mL, and raise it by 0.5 or 1 μg/mL increments until loss of consciousness (18, 19). In that case, the concentration needed to lose consciousness serves as an initial "calibration" point for that particular patient. Patient response during tube insertion and surgical incision serves as further "calibration" points for individual titration (19). Older and sicker patients most often require less propofol and should be induced starting with lower target concentrations, generally ranging between 1 and 2 μg/mL (20).

3) *What is the best target for the opioid ?*

The remifentanil Ce that blunts cardiovascular responses to tracheal intubation generally ranges between 3 and 6 ng/mL during propofol anesthesia (21). A remifentanil Ce of 2.1 ng/mL has been proposed for skin incision (21), but a remifentanil Ce between 3 and 10 ng/mL is required to abolish the hemodynamic response during more intense surgical stimulation. If remifentanil TCI is not available, manual infusions within the range of 0.1 to 0.3 μg/kg/min will generate equivalent remifentanil Ce. Equivalent sufentanil plasma concentrations range between 0.1 and 0.8 ng/mL (22).

4) *What is the best propofol-opioid combination ?*

TCI anesthesia allows individual anesthesia titration during induction and independent titration of the hypnotic and opioid concentrations throughout the entire surgical procedure. It facilitates smooth anesthesia induction and subsequent maintenance with the same agents.

Drug interactions between hypnotic and opioid drugs are mostly synergistic and an optimal combination for best probability of no response to intubation and during surgical stimulation is dependent on the patient's physiological and pharmacogenetic characteristics, and on the type of drugs used. Re-

cent studies of a series of remifentanil – propofol interaction models demonstrate that these models adequately predict responses to selected pertinent events during elective surgery (23). Reference points of the balance between the intensity of the noxious stimulus and the anti-nociceptive opioid level can be obtained at tracheal intubation and skin incision (24).

The anesthesiologist can record the plasma or effect site concentrations of the hypnotic and opioid combination at patient loss of consciousness, at the insertion of the laryngeal mask or endotracheal tube, at skin incision, and when there is no response to surgical stimulation. Thereafter, he/she can adjust concentrations of both components to prevent any further patient's hemodynamic or somatic responses during maintenance. These reference points are also helpful in choosing the appropriate IV anesthetic drug level to facilitate rapid recovery from TCI anesthesia.

No TCI dedicated pumps are commercially available for ketamine, alpha blocking agents and benzodiazepines. These 3 classes of anesthetic drugs are often combined with propofol in modern TIVA techniques. The synergy of these drugs allows reducing opioid consumption and risk of hyperalgesia.

Conclusion

Adopting these tips, tricks, safeguards and recommendations for the daily clinical practice of TIVA and TCI will most probably reduce the risk of intra-operative incidents related to the delivery of intravenous anesthetic agents. Safety and security remain the priority in our profession. Good clinical practice should be audited, and staffs encouraged reporting encountered incidents.

References

1. Vanlersberghe C., Camu F., *Propofol*, Handb. Exp. Pharmacol., **182**, 227-52, 2008.
2. Van den Nieuwenhuyzen M., Engbers F., Vuyk J., Burm A., *Target-Controlled Infusion Systems, role in Anaesthesia and Analgesia*, Clin. Pharmacokinet., **38** (2), 181-190, 2000.
3. Keay S., Callander C., *The safe use of infusion devices. Continuing education in Anaesthesia*, Crit. Care. Pain J., **4**, 81-85, 2004.
4. Schraag S., Flaschar J., *Delivery performance of commercial target-controlled infusion devices with Diprifusor (R) module*, Eur. J. Anaesthesiol., **19**, 357-360, 2002.
5. Guaranteeing Drug Delivery in Total Intravenous Anaesthesia. Safe Anaesthesia Liaison Group. National Patient Safety Agency report. AAAGBI Anaesthesia News.
6. Decaudin B., Dewulf S., Lannoy D., Simon N., Secq A., Barthélémy C., Debaene B., Odou P., *Impact of multiaccess infusion devices on in vitro drug delivery during multi-infusion therapy*, Anesth. Analg., **109** (4), 1147-55, 2009.
7. Lovich M. A., Doles J., Peterfreund R. A., *The impact of carrier flow rate and infusion set dead-volume on the dynamics of intravenous drug delivery*, Anesth. Analg., **100** (4), 1048-55, 2005.
8. Lovich M. A., Peterfreund G. L., Sims N. M., Peterfreund R. A., *Central venous catheter infusions : A laboratory model shows large differences in drug delivery dynamics related to catheter dead volume*, Crit. Care Med., **35** (12), 2792-8, 2007.
9. Moss D. R., Bartels K., Peterfreund G. L., Lovich M. A., Sims N. M., Peterfreund R. A., *An in vitro analysis of central venous drug delivery by continuous infusion : the effect of manifold design and port selection*, Anesth. Analg., **109** (5), 1524-9, 2009.
10. Marsh B., White M., Morton N., Kenny G. N., *Pharmacokinetic model driven infusion of propofol in children*, Br. J. Anaesth., **67** (1), 41-8, 1991.
11. Schnider T. W., Minto C. F., Shafer S. L., Gambus P. L., Andresen C., Goodale D. B., Youngs E. J., *The influence of age on propofol pharmacodynamics*, Anesthesiology, **90** (6), 1502-16, 1999.
12. Minto C. F., Schnider T. W., Egan T. D., Youngs E., Lemmens H. J., Gambus P. L., Billard V., Hoke J. F., Moore K. H., Hermann D. J., Muir K. T., Mandema J. W., Shafer S. L., *Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development*, Anesthesiology, **86** (1), 10-23, 1997.
13. Gepts E., Shafer S. L., Camu F., Stanski D. R., Woestenborghs R., Van Peer A., Heykants J. J., *Linearity of pharmacokinetics and model estimation of sufentanil*, Anesthesiology, **83** (6), 1194-204, 1995.
14. Absalom A. R., Mani V., De Smet T., Struys M. M., *Pharmacokinetic models for propofol – defining and illuminating the devil in the detail*, Br. J. Anaesth., **103** (1), 26-37, 2009.
15. White M., Kenny G. M., Schraag S., *Use of target controlled infusion to derive age and gender covariates for propofol clearance*, Clin. Pharmacokinet., **47** (2), 119-127, 2008.
16. Ingrande J., Brodsky J. B., Lemmens H. J. M., *Lean Body Weight Scalar for the Anesthetic Induction Dose of Propofol in Morbidly Obese Subjects*, Anesth. Analg., **113**, 57-62, 2010.
17. Hendrickx J. F., Eger E. I 2nd., Sonner J. M., Shafer S. L., *Is synergy the rule ? A review of anesthetic interactions producing hypnosis and immobility*, Anesth. Analg., **107** (2), 494-506, 2008.
18. Irwin M. G., Hui T. W., Milne S. E., Kenny G. N., *Propofol effective concentration 50 and its relationship to bispectral index*, Anaesthesia, **57** (3), 242-8, 2002.
19. Milne S. E., Troy A., Irwin M. G., Kenny G. N., *Relationship between bispectral index, auditory evoked potential index and effect-site EC50 for propofol at two clinical endpoints*, Br. J. Anaesth., **90** (2), 127-31, 2003.
20. Lysakowski C., Elia N., Czarnetzki C., Dumont L., Haller G., Combescure C., Tramer M. R., *Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients*, Br. J. Anaesth., **103** (3), 387-93, 2009.
21. Albertin A., Casati A., Federica L., Roberto V., Travaglini V., Bergonzi P., Torri G., *The effect-site concentration of remifentanil blunting cardiovascular responses to tracheal intubation and skin incision during bispectral index-guided propofol anesthesia*, Anesth. Analg., **101** (1), 125-30, 2005.

22. Derrode N., Lebrun F., Levron J. C., Chauvin M., Debaene B., *Influence of peroperative opioid on postoperative pain after major abdominal surgery : sufentanil TCI versus remifentanil TCI. A randomized, controlled study*, Br. J. Anaesth., **91**, 842-9, 2003.
23. Bouillon T. W., Bruhn J., Radulescu L., Andresen C., Shafer T. J., Cohane C., Shafer S. L., *Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy*, Anesthesiology, **100** (6), 1353-72, 2004.
24. Johnson K. B., Syroid N. D., Gupta D. K., Manyam S. C., Egan T. D., Huntington J., White J. L., Tyler D., Westenskow D. R., *An evaluation of remifentanil propofol response surfaces for loss of responsiveness, loss of response to surrogates of painful stimuli and laryngoscopy in patients undergoing elective surgery*, Anesth. Analg., **106** (2), 471-9, 2008.