TIVA for Neurosurgery

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13.1 Introduction

A tailored anesthesia constitutes a major goal of the modern anesthetic practice based on the patient's individual needs, surgical procedure and outcomes. To better achieve it, the modern anesthesiologist should use drugs with a predictable and favorable profile: a rapid onset and offset, safe and rapid induction, early recovery, easily titratable and without - or minimal - adverse or unwanted effects.

Pending the development of new and "almost-ideal" drugs, the emergence and improvement of systems and devices that allow their safe and accurate delivery, have contributed to the development of our practice.

Hypnotics and opioid drugs of short duration of action, such as propofol and remifentanil, along with target-controlled infusion systems (TCI) have increased the popularity of total intravenous anesthesia (TIVA) and enabled a tailored technique even in different settings such as ambulatory and office-based anesthesia [1].

Thus, the debate continues on intravenous and inhalation anesthesia regarding well-defined clinical endpoints. These are mainly related to the speed and recovery of anesthesia, hemodynamic changes, operative conditions, postoperative nausea and vomiting, recovery of psychomotor and cognitive function, and discharge from hospital.

13.2 TIVA Advantages

TIVA's increasing popularity and its several advantages in the peri-operative setting are listed in Table 13.1.

Table 13.1 TIVA advantages

Less pollution
Control of sedation before induction and at emergence
Safe and accurate titration of drugs
No conflict between airway access and drug delivery
Hypoxic vasoconstrictor reflex intact
No change in surfactant production
No renal toxicity due to fluoride ions
Safe in malignant hyperthermia
Less postoperative nausea and vomiting (PONV)
Postoperative analgesia titration
Less postoperative pain
Early postoperative patient well-being
Less imunossupression

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Beyond the well-known presented clinical endpoints, patient satisfaction is increasingly valued and it has been suggested to be higher after TIVA–TCI, mainly due to the lower incidence of PONV [2].

Furthermore, research on long-term outcomes has shown that intravenous anesthesia with propofol may be more favorable concerning cancer recurrence after surgery [3]. Although several contradictory results have been published concerning immunosuppression, it seems that propofol attenuates surgical stress response without impairment of natural killer cell activity and leading to less significant immunosuppression [4].

Aware of the advantages described, economic impact has been a subject of great interest with insufficient studies until now. Although TIVA–TCI is generally considered more expensive, the associated costs are mainly related to the equipment and consumables. Therefore, all costs and benefits should be considered, related not only to the technique but also the institution, the patient, and the society [5].

Nevertheless, we should not forget the safety and easy titration of volatile anesthetics and recognize the merits of both techniques [6]. Clear indications for the use of each technique are lacking and the choice seems to be more related to the individual experience and familiarity with the technique than based on published studies, without forgetting the availability of the equipment.

13.3 Anesthetic Pharmacology and CNS

For a better understanding of the advantages and disadvantages related to different techniques, the main characteristics of the most commonly used anesthetics drugs are summarized in Tables 13.2 and 13.3.

Propofol has rapid onset and offset, decreases cerebral blood flow (CBF) and cerebral metabolic rate ($CMRO_2$) dose-dependently, with a reduction in intracranial pressure (ICP).

The most commonly used volatile agents, sevoflurane and desflurane, increase CBF dose dependently for MAC greater than 1, with low

Table 13.2 Effects of intravenous agents respectively on CBF, $CMRO_2$, AND ICP

	CBF	$CMRO_2$	ICP
Propofol	- - -	- - -	- - -
Barbiturates	- - -	- -	- -
Etomidate	- - -	- - -	- - -
Ketamine	+ + +	+ + or =	+ + or + + +
Opioids	- or + or =	- - or =	+ or =
Benzodiazepines	- -	- -	- -
Dexmedetomidine	- -	- - or =	=

+ slight increase, + + increase, + + + marked increase, = no change, - slight decrease, - - decrease, - - - marked decrease

Table 13.3 Effects of volatile agents respectively on CBF, $CMRO_2$, AND ICP

	CBF	$CMRO_2$	ICP
Sevoflurane	- - or = or +	- - or - - -	+ + or + or =
Desflurane	- - or + +	- - -	+ + or =
Isoflurane	+ + or =	- - -	+ or + + or =
N_2O	+ + +	+ + or =	+ + +
Xenon	- - (gray) + + (white)	- -	+ + or =

+ slight increase, + + increase, + + + marked increase, = no change, - slight decrease, - - decrease, - - - marked decrease

$CMRO_2$ affecting the CBF–$CMRO_2$ coupling due to cerebral vasodilation. This is more sustained in patients with impairment of cerebral compliance.

Because of its effects on cerebral physiology, propofol has been suggested as the ideal anesthetic for neurosurgery providing better operating conditions, while TIVA is the elected technique [7].

13.4 TCI and Modern Practice of TIVA

TCI systems have made TIVA simpler, easier, and safer. The practice of target-controlled anesthesia is based on fundamental pharmacokinetic and pharmacodynamic concepts which deserve a detailed review.

13.4.1 The Compartment Model

Pharmacokinetic models describe a drug's behavior in the body. For most anesthetic drugs, a two or three compartment model can describe it with great accuracy (Fig. 13.1).

In the three compartment model, as shown above, after the drug is injected into the central compartment (V_1), it will have rapid distribution to the second compartment (V_2), slow distribution to the third compartment (V_3), and also redistribution between them. The intercompartmental time constants (K_{12}, K_{21}, K_{23}, K_{32}) describe the proportion of the drug that is undergoing each one of these processes during a unit of time (min^{-1} or h^{-1}). Drug elimination by metabolism from the central compartment corresponds to the constant K_{10}.

It is important to notice that these volumes have no real anatomical correlation. They are theoretical volumes that can be remotely thought as the blood volume (V_1), a "vessel rich" compartment (V_2) and a "vessel poor" compartment (V_3).

In each model, the size of the volumes of distribution reflects the solubility of the drug in that specific compartment. The more the drug is soluble, the higher is the volume.

For pharmacokinetic/pharmacodynamic modeling, an effect-site compartment can be added. Due to its negligible volume, the rate constants for movement in and out of this compartment are the same ($K_{1e} = K_{eo}$).

In the past decades, pharmacokinetic models have been developed and improved, allowing better understanding of the behavior of different drugs and making possible the adjustment to the individual kinetics. These models are the result of arterial or venous sampling with measurement of blood concentration of a drug, after a bolus or infusion, in well-defined populations, using sta-

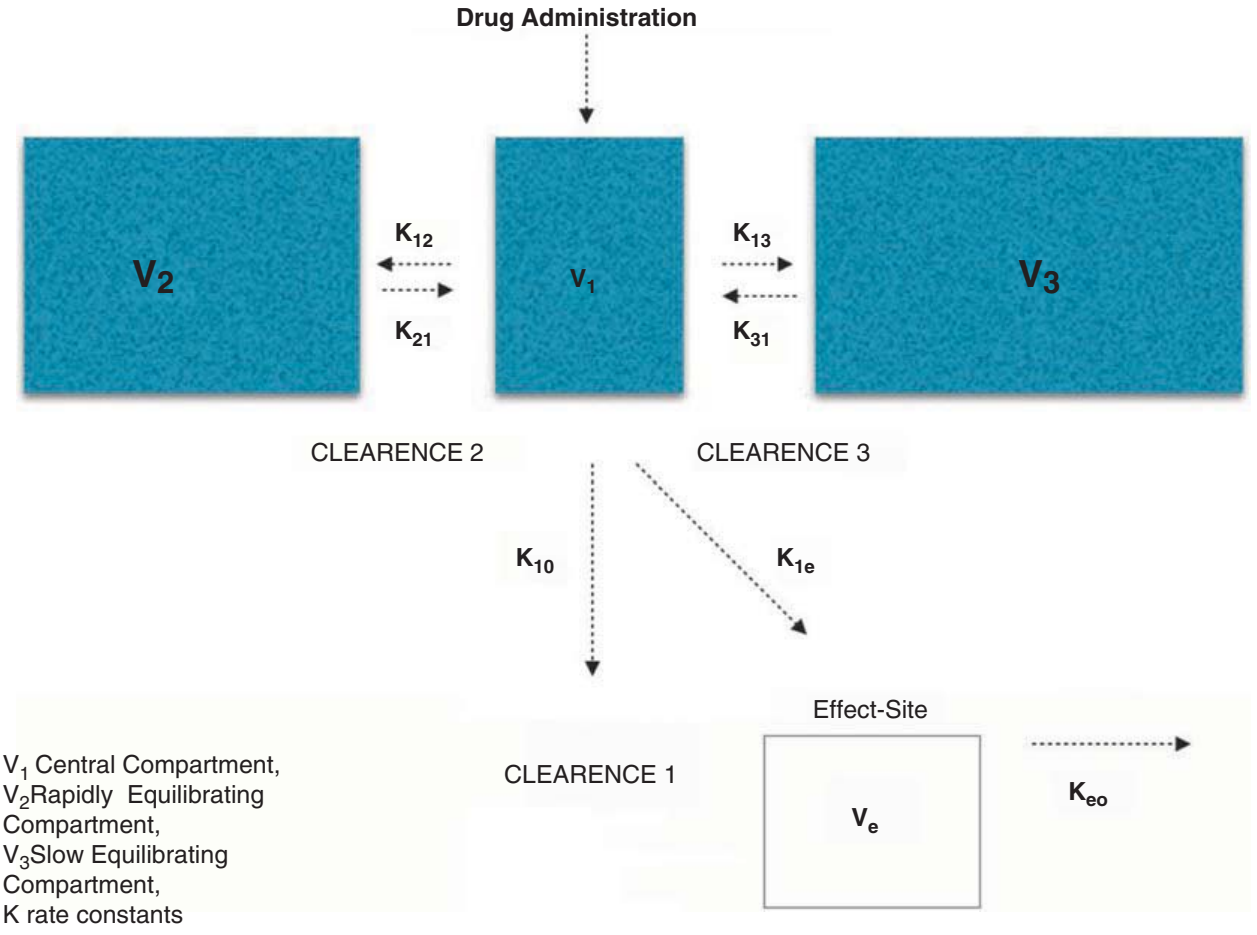

Fig. 13.1 Three compartment pharmacokinetic model with an effect-site compartment

tistical analysis. By knowing the rate constants for each drug, it is possible to predict the concentration in different compartments after a bolus injection of the drug.

TCI systems incorporate this information and, based on individual parameters, allow to predict plasmatic and/or effect-site concentrations (C_p/C_e) controlling drug administration by the infusion pump.

13.4.2 Pharmacokinetic Concepts

Volume of Distribution (V_d) is the volume in which the drug is distributed and its value depends on the time of calculation. Time zero relates to V_1 and at steady state is the sum of V_1, V_2 and V_3. Generally, it can be calculated knowing the dose present in the body (D) and its plasma concentration (C):

$$V_d = D / C \tag{13.1}$$

Although it reflects the distribution of a drug in the body, V_d can exceed the anatomical body volume several times. For e.g., if a drug accumulates in tissues, it will have a low plasma concentration and a consequently high V_d. Drugs with a small V_d are those mainly confined to the intravascular fluid.

This concept allows calculation of the loading dose that the TCI system will deliver to achieve the desired target concentration (C_e or C_p), according to the calculated V_d:

$$\text{Loading Dose} = C \cdot V_d \tag{13.2}$$

If another bolus is required to increase the target concentration,

$$\textit{New}\,\text{Loading Dose} = \left(Cf - Ci\right) \cdot V_d; \tag{13.3}$$

Cf – final concentration, *Ci* – initial concentration.

Clearance (*Cl*) describes the volume in which the drug is eliminated during a unit of time (mL/min or mL/hr). This particular setting also describes the drug movement between compartments. It can be calculated as:

$$\text{Clearance} = K_{el} \cdot V_d; \tag{13.4}$$

K_{el} – elimination rate constant.

The maintenance infusion rate of TCI systems will compensate the clearance of the drug exciting the body. It is defined as the concentration at steady state multiplied by the clearance value (*Cl*).

$$\begin{aligned}&\text{Maintenance infusion rate}\\ &\textit{at}\,\text{steady} - \text{state} = C_{ss} \cdot Cl\end{aligned} \tag{13.5}$$

These two concepts can explain the basis of TCI systems, though there are other concepts regarding pharmacokinetics of infusions that assume big importance in this clinical setting.

Half Life ($t_{1/2}$) is the time taken for the concentration of a drug to drop by half its value. However, since most drugs are distributed in more than one compartment and clearance from each one occurs at different rates, the drug will have more than one $t_{1/2.}$ The actual $t_{1/2}$ of a drug is the sum of the individual half-lives.

For this reason, it is preferable to use the *context-sensitive half-time.* This is the time required for a drug's blood concentration to decrease to 50% its previous value after stopping an infusion of a given duration. *Decremental time* is a similar concept that defines the time required for blood concentration to decrease to a desired percentage.

Both concepts are useful predictors of drug concentration decline after an infusion is stopped. TCI systems provide a calculation of the time needed for the measured concentration to decrease to a definable concentration at which recovery is expected.

13.4.3 Pharmacodynamic Concepts

The brain is the site where anesthetic drugs exert their clinical effect, which defines it as the effect site. For this reason it becomes obvious that the main effect is delayed as well as the drug concentration at the effect site when compared to the plasma peak concentration. *Hysteresis* represents this time delay between plasma compartment and effect-site compartment. Mathematically, the time taken for blood–effect-site equilibration is described by the rate constant K_{e0} which is different for different drugs.

Time to peak effect (TTPE) is the time delay between a bolus and maximum effect-site concentration and is independent of size of bolus (Fig. 13.2).

*T*1/2 K_{e0} is the time taken for the drug concentration in the effect site to reach half of the concentration in the blood and can be clinically more useful than K_{e0}. Knowing the K_{e0} and TTPE makes it possible to "target" the effect-site concentration.

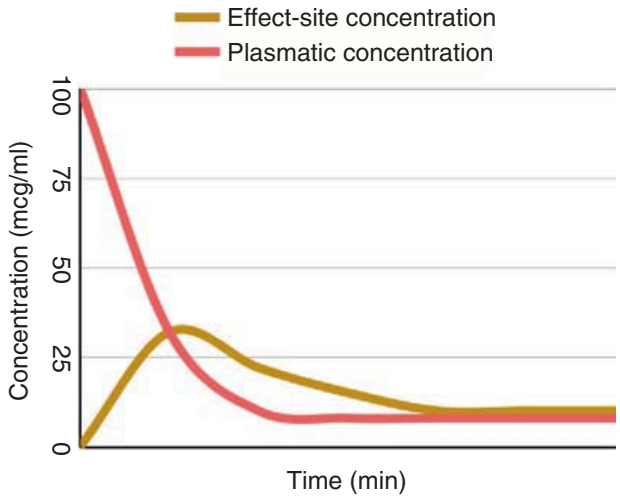

Fig. 13.2 Graphic representation of time to peak effect for a bolus dose of a drug: corresponds to the point where the blood and effect-site concentration curves cross

13.4.4 Target-Controlled Infusion

A target-controlled infusion is an infusion controlled as fast and safe as possible in order to achieve and maintain a defined concentration of a drug in a site of interest as well as the wanted clinical effect.

In clinical practice, the anesthesiologist programs the TCI set-up using the computer interface. First, sets the patient data and then defines the target concentration, plasmatic or in the effect site (C_p/C_e), based on the desired effect and adjusted to the patient's clinical response. The computer system with its mathematical algorithm calculates the specific parameters for each patient, as *Vd* and *Cl*. Accordingly, the infusion pump delivers the bolus dosage and the infusion rates required to achieve and maintain the desired target concentration at steady state. Continuous automatic calculations are made to adjust the infusion rate to the distribution and elimination of the drug. To compensate these processes, the software calculates three superimposed infusion rates decreasing gradually. Target concentrations should be continuously titrated and adjusted to the clinical response.

A TCI system (Fig. 13.3) is composed of a computer, a user interface, and an infusion device. The interface allows the data input according to the pharmacokinetic model incorporated and

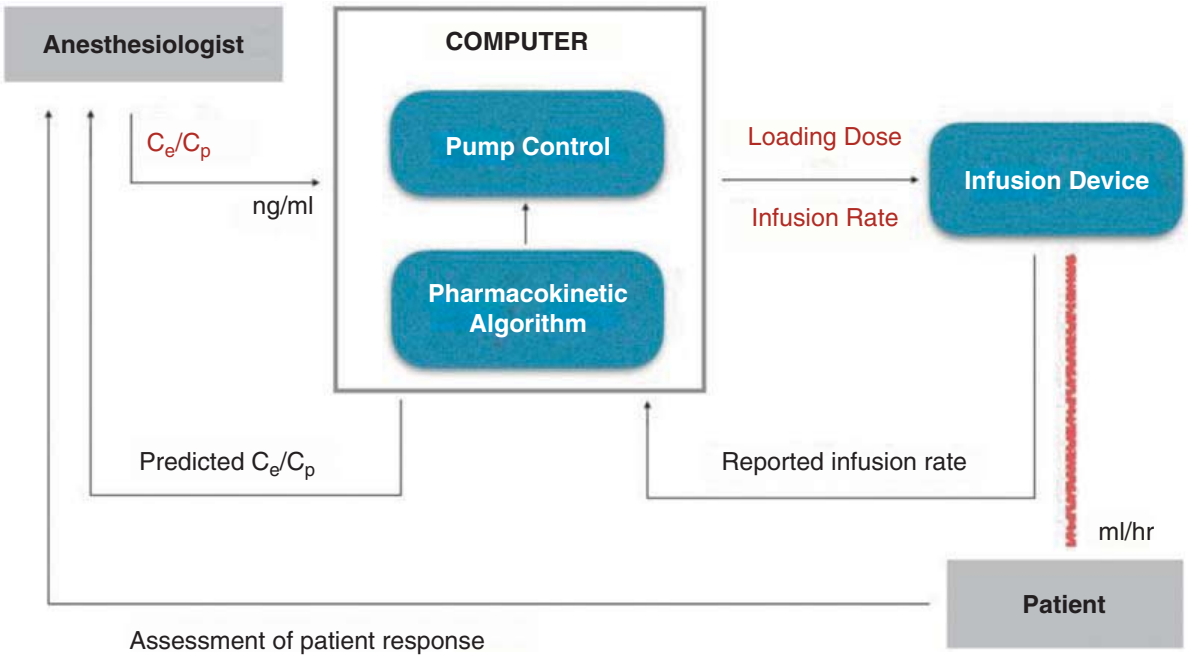

Fig. 13.3 Components of a TCI System

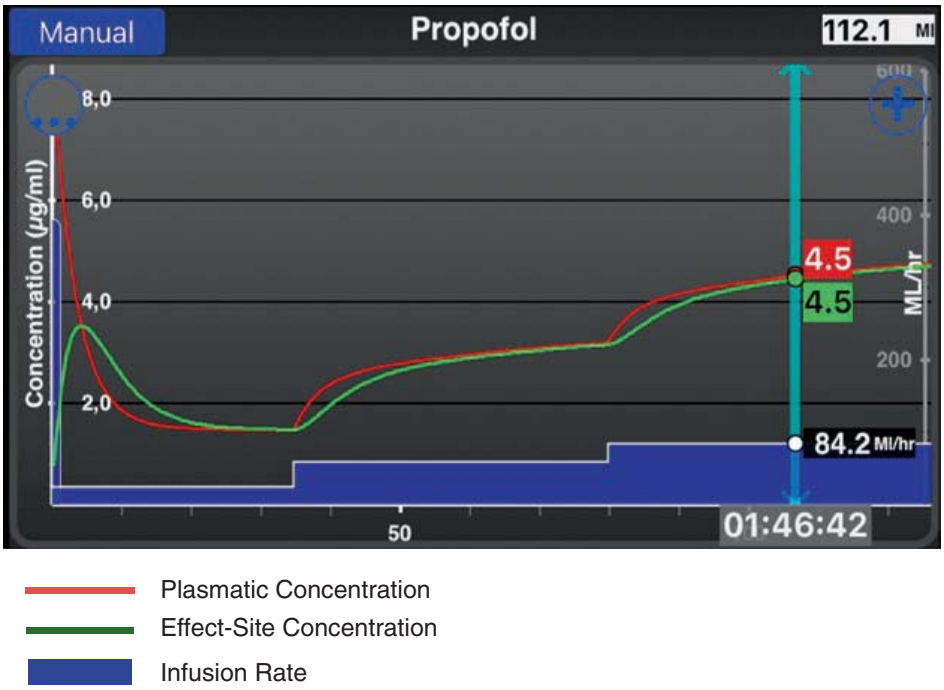

Fig. 13.4 Manually controlled infusion of propofol after an initial bolus

gives numeric and/or graphic information. The computer controls the interface, implements the pharmacokinetic models, controls the infusion device and implements warning systems.

It is important to keep in mind that when using a TCI system, although the user can manage the target concentration, no real concentrations are measured during the infusion and that is why they are called "open-loop" systems.

13.4.4.1 TCI Versus Manual Perfusions

When using a manually controlled infusion, by administering drugs at a fixed rate, it will take a long time to reach steady state, approximately, four to five half-lives, until the drug equilibrates throughout all the tissues in the body. For this reason, the blood concentrations will change very slowly and changes in the infusion rate will not lead to significant changes in plasmatic or effect-site concentration for some time. Also, clinical effect will take too long (Fig. 13.4).

That's why a system of bolus dosing and variable infusion rates is more suitable and effective to better control drug concentration and achieve the desired effect.

However, if a bolus is given and perfusion is controlled randomly by the operator, these doses will be difficult to calculate and to adjust for a rapid and safe control of the target concentrations, potentiating adverse or undesirable effects.

13.4.4.2 Propofol Blood-Targeted TCI

In TCI systems, after setting the desired target concentration, the infusion device will deliver a bolus to quickly fill the central compartment (V_1) with gradual increase in blood concentration. When the system calculates that the targeted blood concentration has been reached, it stops and then starts an infusion at a lower rate. When the operator decreases the target concentration, the system switches off the infusion and starts only when the predicted concentration has reached the target concentration, at a lower rate (Fig. 13.5). If a bolus is delivered to achieve a higher concentration, the system will then adjust the infusion rate to achieve and maintain a new steady-state concentration.

13.4.4.3 Propofol Effect-Site Targeted TCI

When choosing effect-site concentration for TCI, the system manipulates the blood concentration to achieve the effect-site target as quickly as possible. Thus, a large bolus is delivered and a faster rise in effect-site concentration can be seen. After

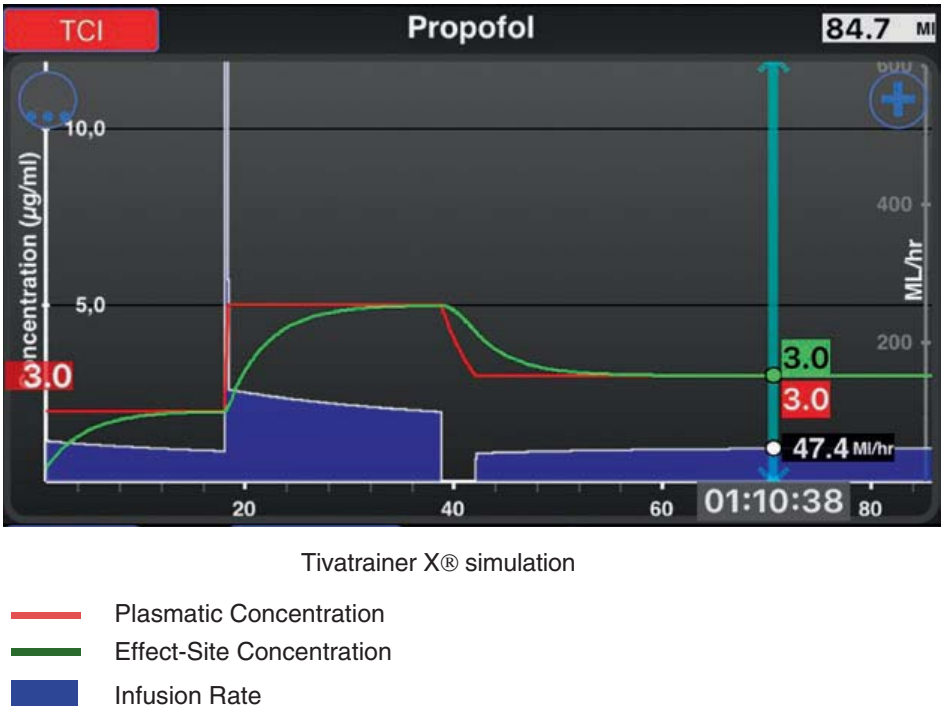

Fig. 13.5 Blood concentration targeted TCI for propofol

the initial bolus, the infusion stops until the declining blood concentration reaches the increasing effect-site concentration. At that point, it restarts at a rate that maintains blood and effect-site concentrations at the desired target concentration. If the target concentration is decreased, the TCI will stop the infusion and effect-site concentration will fall due to the movement of propofol down its concentration gradient out of the effect-site. When the new effect-site concentration has been reached, a different infusion rate starts maintaining a new equilibrium. Thereafter, if a higher effect-site concentration is defined, the system will deliver another bolus followed by the appropriate infusion rate.

13.4.4.4 Propofol and Remifentanil TCI

Pharmacodynamic interactions are common and very important in clinical setting. Total intravenous anesthesia combining the use of propofol with remifentanil shows a synergism meaning that lower concentrations of each drug are needed to achieve the desired effect [8]. As shown in Fig. 13.6, the target concentration of propofol required for maintenance of adequate anesthesia decreases with increasing concentrations of remifentanil.

This synergistic effect allows the combination of moderate doses resulting in optimal concentrations for anesthesia, easily titratable, with rapid awakening times [9]. Although it has a safety margin for side effects, some adverse effects also act synergistically, such as hypotension or apnea, and care must be taken to provide the optimal concentrations and avoid overdosing (Fig. 13.7).

13.4.4.5 Setting the TCI Pump

For a better and safer practice of TIVA/TCI, some recommendations should be followed: (recomendations) Always keep in mind, the paradigm shift of mL/h to ng/mL, while thinking in the individual kinetics and not in the population.

13.5 TIVA and Brain Surgery

In the particular case of neuroanesthesia, the main goals are related with the decrease in cerebral metabolism, maintaining autoregulation ($PaCO_2$ and MAP) and normal intracranial pressure, and also to provide optimal operative conditions with electro-neurophysiological monitoring and a rapid offset preserving cognitive functions.

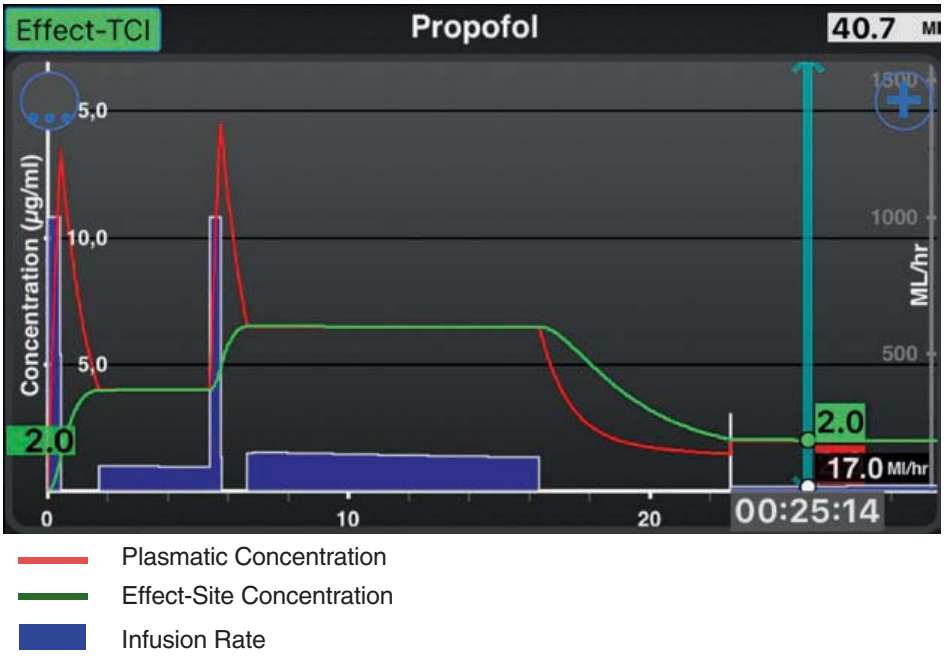

Fig. 13.6 Effect-site concentration targeted TCI for propofol

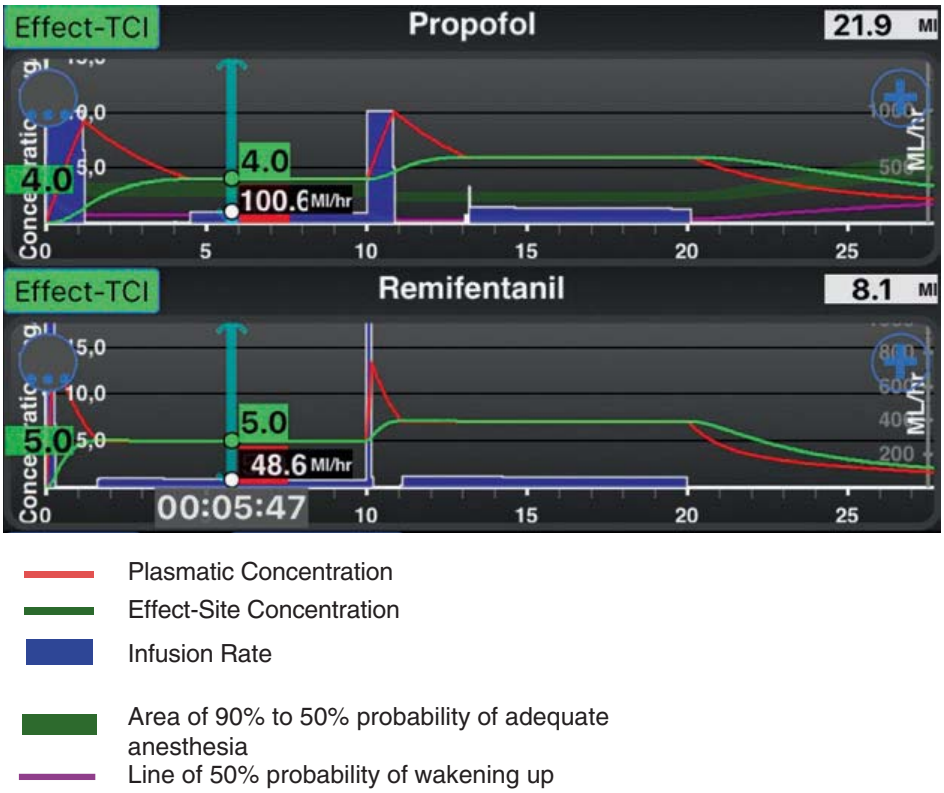

Fig. 13.7 Propofol and remifentanil TCI

Giving particular importance to situations with impaired cerebral autoregulation, e.g. TBI or space-occupying lesions, TIVA seems to be more suitable in those cases [10].

A recently published systematic review and meta-analysis concluded that mean ICP values were lower and cerebral perfusion pressure (CPP) values were higher with propofol-maintained anesthesia [11].

- Programming the pump should be made by an anesthesiologist familiarized with the settings and differences of each pharmacokinetic model;
- Prepare an adequate intravenous system;
- Know the covariates (age, gender, weight, height and lean body mass), its limitations regarding the obese and the extremes of age and the concomitant variations of pharmacokinetics and pharmacodynamics;
- Check the loading doses, steady-state infusion rates and measured concentrations;
- Monitor the targeted effect, e.g., using monitors of processed EEG;
- Titrate the target concentration according to your monitoring and surgical stimulation;
- Know the pharmacologic interactions between drugs used together during TIVA/TCI.

Beneficial effects of anesthetic drugs as neuroprotectants have been inconclusive [12], although a possible role of intravenous agents was recently appraised [13]. Very recently, sevoflurane and isoflurane were shown to induce structural changes in brain endothelial cells, increasing brain barrier permeability, leading to disturbed neuronal function [14].

A suggested approach is to use indirect evidence of different outcomes in fragile brains after exposure to different anesthetic drugs with translational application to the fragile brain under surgery.

Anesthesia-induced developmental disturbances with long-term poor outcomes in young mammalian brain are under debate and research in the last decade with contradicting evidence [15–18] implicating volatile agents, nitrous oxide, ketamine and, in a less extent, propofol. However, a possible protective effect of propofol may be inferred after Jacob et al. [19] showed different cerebral metabolic signatures for sevoflurane and propofol in children undergoing magnetic resonance imaging during sevoflurane- or propofol-based anesthesia, with higher levels of cerebral lactate and glucose in children under sevoflurane anesthesia and a strong and significative association between these metabolites and the occurrence of emergence delirium. Assuming that immediate cognitive disturbances after general anesthesia like delirium or emergence agitation are the result of changes in cerebral physiology, we cannot also forget that propofol significantly decreases the severity and incidence of emergence agitation and delirium in pediatric patients [20], supervening the idea that TIVA will supercede inhalational anesthesia [21].

Sevoflurane has also shown to be associated with negative postoperative behavioral changes in children undergoing adenotonsillectomy while the incidence and severity of cognitive changes were significantly lower when children had propofol-based anesthesia [22].

Also, in vitro studies in animals show that inhalational anesthesia can lead to an increase in amyloid beta peptide deposition as in Alzheimer's disease, which may be related to postoperative cognitive disorder (POCD) [4].

Whether these findings are significant we still don't know but, at least, they trigger doubts about the cerebral health after exposure to volatile agents [23].

A very special case where TIVA–TCI is particularly useful is when an awake patient is required to improve neurosurgical outcome: resection of a tumor or an epileptic focus close to an eloquent area and functional neurosurgery for movement disorders are the paradigm of awake neurosurgery. [24–27]

Although several anesthetic techniques have been described, there is a trend toward the use of a asleep–awake–asleep or asleep–awake approach with TCI of propofol and remifentanil titrated by processed EEG monitors and scalp block, using a laryngeal mask and controlled

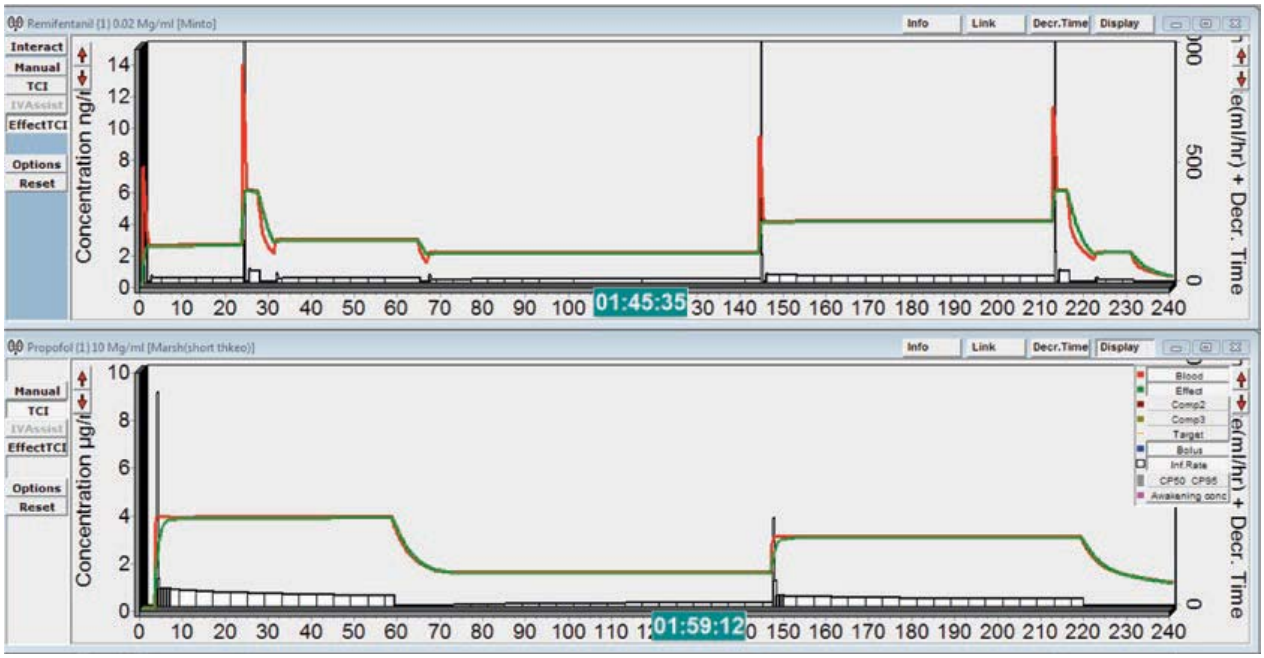

Fig. 13.8 Asleep–awake–asleep technique with propofol and remifentanil TCI

ventilation during craniotomy or, more recently, dexmedetomidine [28–32].

Figure 13.8 shows an example of TCI of propofol and remifentanil for craniotomy with intraoperative awakening for resection of a tumor close to Broca area.

13.6 TIVA and Spine Surgery

As mentioned before, anesthetic drugs used during brain and spine surgery should allow electroneurophysiological monitoring, as electroencephalogram and evoked potentials. During spine surgery, evoked potentials allow to control the integrity of neural pathways. While volatile agents may decrease amplitude and prolong latency of somatosensory evoked potentials (SSEP) in a dose-dependent manner, propofol and other intravenous agents such as dexmedetomidine allow better preservation of evoked responses [33–39].

Propofol and intravenous anesthesia is also associated with a smoother emergence after spine surgery, with less coughing and hemodynamic response and reliable neuro-electrophysiological monitoring [10, 40, 41].

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