Practical Trends in Anesthesia and Intensive Care 2022

Davide Chiumello
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Part I

Anesthesia

TIVA and TCI in Modern Anesthesia

1

Franco Cavaliere and Carlo Cavaliere

General anesthesia is characterized by reversible depression of central nervous system functions, with the goal of inducing loss of consciousness, analgesia, amnesia, abolition of neurovegetative responses to stimuli, immobility, and, in some cases, abolition of muscle tone. Over the years, the pharmacological toolbox available to the anesthesiologist has increased considerably. There are a variety of drugs that can be used, some administered by inhalation because they are in the gas or vapor state under ambient conditions, and others administered intravenously. Totally intravenous anesthesia (TIVA: Total IntraVenous Anesthesia) uses only intravenous anesthetics; inhalational anesthesia employs anesthetic vapors; balanced anesthesia, the most widely used, uses both routes. Target-Controlled Infusion (TCI) is a technique for administering intravenous anesthetics that uses advanced infusion pumps, which can autonomously vary the infusion rate to maintain a constant concentration of anesthetic set by the operator in the plasma or effector site; the software with which the pump is equipped continually reevaluates the amount of drug to be infused based on a pharmacokinetic model. Closed-Loop Anesthesia is an anesthesia technique using the TCI method, in which the anesthesiologist does not set the concentration of the anesthetic but the magnitude of the desired effect, e.g., the level of depth of anesthesia as measured by the Bispectral index (BIS). In this mode, the software changes the target plasma concentration based on data from the monitoring system. Table 1.1 shows some important dates in the development of intravenous anesthesia [1].

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Table 1.1 Some important dates in the development of intravenous anesthesia

Invention of the syringe, A. Wood, C. G. Pravaz	1853
Intravenous chloral hydrate to produce general anesthesia, P. C. Oré	1872
Synthesis of sodium thiopental, E. H. Volwiler, D. L. Tabern	1934
Development of propofol, JB Glen	1973
Commercialization of propofol, Astra-Zeneca plc	1986
Commercialization of remifentanil, Glaxo Wellcome Inc.	1996

1.1 Indications for the Use of TIVA

The choice of anesthetics and thus the technique, inhaled, intravenous, or balanced, depends on the characteristics of the patient, the type of surgery, and the preferences of the anesthesiologist. The use of TIVA is often motivated by the purpose of avoiding environmental pollution related to the release of anesthetic gases or vapors into the ambient air, although in today's operating rooms air pollution is prevented by the presence of outdoor elimination systems for gases exhaled by the patient. However, the problem of the harmful effects of nitrous oxide on the environment remains. This anesthetic is in fact a more harmful greenhouse gas than carbon dioxide, which can remain in the atmosphere without degrading for many years and which damages the ozone layer in the stratosphere [2].

The main indication for the use of TIVA is the need to avoid inhaled anesthetics. An example is anesthesia in patients at risk of malignant hyperthermia, because anesthetic vapors can trigger this hypermetabolic response of skeletal muscles [3], and in those with long QT syndrome, in whom sevoflurane can trigger ventricular torsion tachycardia [4]. Inhalational anesthetics should also be avoided in patients at high risk for postoperative nausea and vomiting (PONV) because their use is associated with a higher frequency of episodes [5]. In neurosurgery, anesthetic vapors can increase intracranial pressure and interfere with neurophysiologic monitoring.

Another indication for the use of TIVA may arise from the environment where anesthesia or sedation is performed. Indeed, the use of anesthetic vapors requires the availability of the appropriate vaporizer and anesthesia equipment. The unavailability of this equipment may force the anesthesiologist to choose totally intravenous anesthesia. This may occur in surgeries performed outside of operating rooms and in cases where the surgical procedure requires moving the patient still under general anesthesia from one setting to another.

1.2 Pharmacokinetics of Intravenous Anesthetics

1.2.1 Peculiarities of Intravenous Anesthetics Versus Anesthetic Vapors

One of the aspects that differentiate intravenous anesthesia from inhalation anesthesia is the lack of parameters to monitor the concentration of anesthetic in the blood. In inhalational anesthesia, in fact, the use of equipment to measure the concentration of anesthetics in the gases exhaled by the patient is widespread. The end-expiratory value corresponds to the concentration in the pulmonary alveoli and is a good estimate of that in arterial blood. This parameter is universally used to express anesthetic potency, and the end-expiratory concentration sufficient to inhibit the patient's response to surgical incision of the skin in 50% of subjects (MAC, Minimal Alveolar Concentration) is one of the parameters that guide the anesthesiologist. In addition, the use of alarms set to the end-expiratory concentration of anesthetic vapors is very useful in preventing awareness, having demonstrated similar effectiveness to monitoring systems based on electroencephalographic signal analysis [6].

A further difference between intravenous and inhalational anesthesia is that anesthetic vapors result in a global depression of the nervous system, offering the possibility of performing single-drug anesthesia, whereas intravenous anesthetics have more selective actions, particularly on the hypnotic and analgesic components. This makes clinical assessment of the depth of anesthesia and degree of analgesia achieved during TIVA more difficult and increases the risk of an inadequate level of hypnosis and intraoperative awareness episodes [7]. Therefore, the use of anesthesia depth monitoring systems based on electroencephalographic signal analysis is indicated in totally intravenous anesthesia [8].

1.2.2 Trend of Plasma Concentration After an Intravenous Bolus

As with anesthetic vapors, the effects of intravenous anesthetics are closely related to their plasma levels [9]. It is in fact from plasma that they reach the effector site by crossing the blood–brain barrier. A concentration in plasma (or even at the effector site) such that there is no response to surgical incision in 50% of subjects (Cp50) is the equivalent of MAC for intravenous anesthetics.

The concentration achieved after administration of an intravenous bolus depends on the initial dilution of the drug within a central compartment, the volume of which is related to body mass and corresponds to the ratio of the plasma concentration achieved to the dose administered. In this sense, the bolus effect is relatively predictable and dose-dependent. In the literature, intravenous dosages are readily available to achieve for a limited period of time a level of anesthesia sufficient to abolish the patient's response to certain standard stimuli, such as those represented by tracheal intubation or surgical incision.

The difficulty arises from the need to maintain sufficiently stable plasma concentrations to achieve consistent levels of hypnosis or analgesia for a prolonged time. After the initial bolus, in fact, the plasma concentration of the anesthetic gradually decreases both because the drug is distributed within the body and because it is eliminated by the excretory organs. To keep the plasma concentration constant, therefore, it is necessary to infuse the amount of drug needed to balance that which leaves the central compartment. A constant-rate intravenous infusion is unsuitable for this purpose because the amount of anesthetic that leaves the central compartment varies, decreasing progressively over time. During TIVA, therefore, adjustments to the infusion rate are necessary and are set by the anesthesiologist, based on clinical and instrumental monitoring of anesthetic effects, or by the TCI systems software based on a pharmacokinetic model.

1.2.3 Distribution in the Organism

If one follows the plasma concentration of an anesthetic after administration of an intravenous bolus, one can see that its decrease does not have a linear trend corresponding to a constant elimination rate and zero-order kinetics (concentration-independent elimination) (Fig. 1.1a). Instead, the time/concentration graph is represented by a curve showing how the rate at which concentration decreases slows down over time (Fig. 1.2). This occurs because the processes that affect the distribution and elimination of most drugs follow order 1 kinetics, in which the speed of the process varies as the concentration of the drug changes. For example, the diffusion of a drug from one compartment of the body to another occurs with a rate that decreases as the concentration in the first compartment decreases. A process that follows kinetics of order 1 is described by an exponential equation and is represented on a linear graph by a curved line (Fig. 1.1b). If, however, a semi-logarithmic

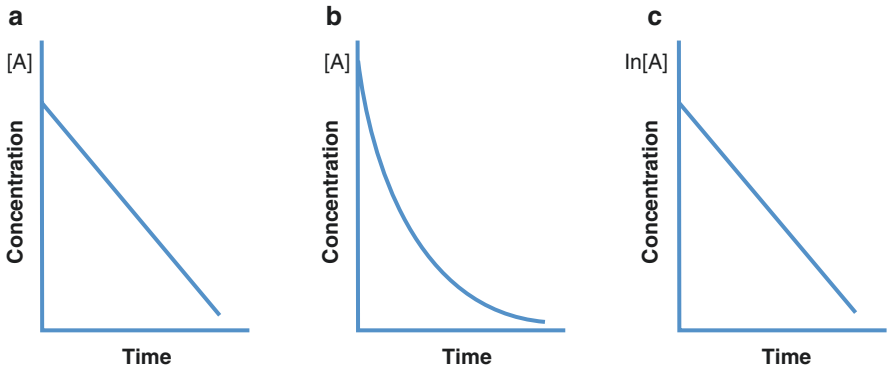

Fig. 1.1 (**a**) Order 0 kinetics: concentration [*A*] decreases at a constant rate over time. (**b**) Order 1 kinetics: concentration [*A*] decreases at a rate that varies over time and depends on [*A*] (linear graph). (**c**) Order 1 kinetics on a semilogarithmic graph

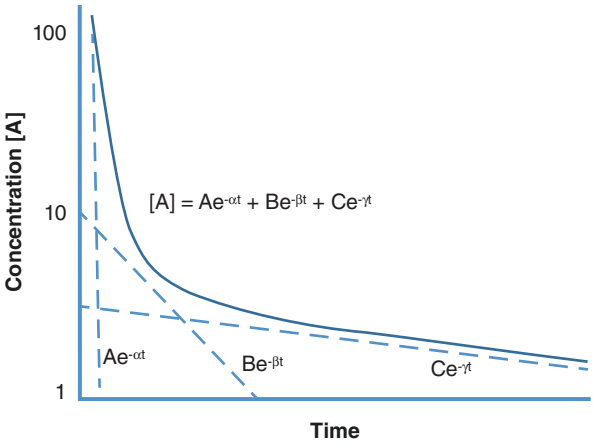

Fig. 1.2 Trend of the plasma concentration of an anesthetic after an intravenous bolus represented on a semilogarithmic plot. The curve can be decomposed into the three components represented by the dashed lines

graph is used, in which the *x*-axis (time) has a linear scale and the *y*-axis (concentration) has a logarithmic scale, the curve becomes a straight line (Fig. 1.1c).

However, the trend in plasma concentration of intravenous anesthetics after an intravenous bolus is more complex than that depicted in Fig. 1.1c and does not assume a linear trend even using a semilogarithmic graph. Figure 1.2 shows the change in concentration of an anesthetic on such a graph. The curve that appears there can be mathematically described by the sum of several exponential functions, represented on the graph by straight lines. In Fig. 1.2, the equation describing the drug concentration trend is given by the sum of three addends and forms the mathematical basis of a tricompartmental pharmacokinetic model.

1.2.4 Tricompartmental Models

The plasma concentration of a drug decreases over time as a result of its distribution within the body and elimination through the excretory organs or metabolism. Distribution in the body exhibits inhomogeneities so that there are better perfused tissues in which the drug diffuses more rapidly and others in which it penetrates more slowly. Each of the three components of the equation shown in Fig. 1.2 describes a process that takes place with kinetics of order 1; these processes have been identified with the diffusion of the drug from the central compartment to a first peripheral compartment (straight line with a greater slope), the slower diffusion of the drug from the central compartment to a second peripheral compartment (straight line with an intermediate slope), and the elimination of the drug through the emunctory organs or metabolism.

Figure 1.3 shows the tricompartmental model that allows a good approximation to describe the processes that influence the pharmacokinetics of intravenous anesthetics. The figure shows a central compartment in which the concentration of the drug is equal to that measurable in plasma and two peripheral compartments, one

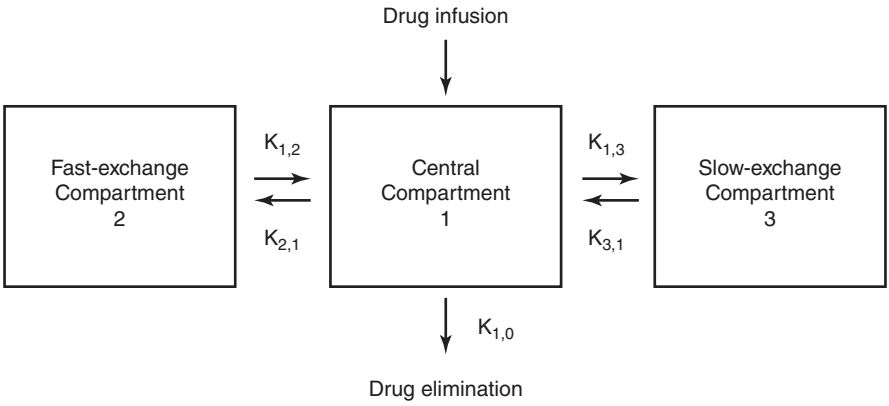

Fig. 1.3 Diagram of tricompartmental model. The drug is administered in the central compartment and from there diffuses to the peripheral compartments and is eliminated through the excretory organs

with rapid and one with slow exchange. These compartments are not real, but only mathematical abstractions. However, the central compartment could be identified with the best-perfused organs; the heart, brain, kidneys, and liver receive about 75% of cardiac output at rest while accounting for about 10% of body weight. The two peripheral compartments balance with the central one at very different rates. The fast-exchange compartment includes tissues that are nevertheless well perfused, mainly muscles. The slow-exchange compartment includes the remaining tissues, such as adipose tissue and bone. The anesthetic administered in the central compartment leaves it by transferring to the two peripheral compartments or through the excretory organs. Diffusion of the drug between the central and peripheral compartments occurs in both directions following the gradient between concentrations. Thus, at the end of an intravenous infusion, the decrease in plasma concentration is slowed by the retrograde diffusion of the anesthetic from the peripheral compartments to the central one.

Figure 1.3 shows the 5 k constants describing the kinetics of drug diffusion and elimination. Each constant is identified by suffix, where $K_{1,2}$ corresponds to the rate of transfer from the central compartment 1 to the fast peripheral compartment 2 and $K_{2,1}$ to the displacement in the opposite direction, $K_{1,3}$ corresponds to the rate of transfer between the central compartment 1 and the slow peripheral compartment, and so on. These constants are derived from the differential equation shown in Fig. 1.2. Table 1.2 presents the mathematical parameters describing the two tricompartmental models most commonly used to perform TCI for propofol; in addition to the k constants, the volumes of the three compartments are given. The differences between the two models highlight the influence of the sample used for database collection and especially the settings chosen by the authors. For example, the volume of the central compartment is a function of body weight in Marsh's model, but not in Schnider's.

Table 1.2 Two tricompartmental models compared

	Marsh [10]	Schnider [11, 12]
*V*1 (L)	0.228 × W	4.27
*V*2 (L)	0.463 × W	18.9–0.391 × (A − 53)
*V*3 (L)	2893 × W	238
*k*10 (min^{-1})	0.119	0.443 + 0.0107 × (W − 77) − 0.0159 × (LBM − 59) + 0.0062 × (H − 177)
*k*12 (min^{-1})	0.112	0.302–0.0056 × (A − 53)
*k*13 (min^{-1})	0.042	0.196
*k*21 (min^{-1})	0.055	[1.29–0.024 × (A − 53)]/[18.9–0.391 × (A253)]
*k*31 (min^{-1})	0.0033	0.0035
k_{eo} (min^{-1})	0.26	0.456
TTPE (min)	4.5	1.69

(modified from Absalom AR et al.) [13]
W weight in kg, *A* age, *LBM* lean mass in kg, *H* height in cm

1.3 Manual Adjustment of Anesthetic Infusion

In general, the use of an intravenous anesthetic requires the administration of an initial bolus, the magnitude of which is based on the desired plasma concentration and the theoretical volume of the central compartment. The plasma concentration is that associated with a given effect based on data available in the literature. For example, the recommended starting dose of propofol in an adult younger than 55 years not premedicated with benzodiazepines or opioids is 2–2.5 mg/kg and is reduced to 1–1.5 mg/kg in an adult older than 55 years or ASA class III–IV. Thereafter, the level of anesthesia achieved should be maintained by continuous infusion so as to balance the drug leaving the central compartment by diffusion to the peripheral compartments or elimination through the excretory organs. As shown, this amount varies over time because transfer to the peripheral compartments slows down as the amount of drug contained within them increases. In the case of propofol, the 10/8/6 rule has been proposed whereby propofol is administered at a rate of 10 mg/kg/h in the first 10 min, 8 mg/kg/h in the second 10 min, and 6 mg/kg/h thereafter [14]. Such a scheme results in a relatively constant plasma concentration of about 3.7 mcg/mL for an intervention lasting 80–90 min. Another proposed scheme involves infusion of 1% propofol at a rate of 600 mL/h for induction of anesthesia until adequate depth is reached followed by an infusion rate corresponding to 6 mg/kg/h [15]. Of course, any scheme still requires careful monitoring of clinical and instrumental signs of depth of anesthesia to tailor the dosage to the individual patient, because of individual variability and association with other anesthetics. Furthermore, maintaining a constant plasma concentration does not allow the depth of anesthesia to be changed to match the intensity of the surgical stimulus during the same procedure. In practice, therefore, the anesthesiologist induces anesthesia of adequate depth by administering one or more boluses and then sets up an

intravenous infusion based on the pharmacokinetics of the anesthetic, verifying throughout the procedure with clinical and instrumental monitoring the maintenance of adequate depth of anesthesia.

1.4 TCI—Target Controlled Infusion

Target Controlled Infusion (TCI) is a technique in which the drug is administered with a pump controlled by software that, at regular intervals, changes the infusion rate so that the concentration set by the anesthesiologist in plasma or at the effector site is rapidly achieved and then maintained constant over time. The software calculates the drug requirement at regular time intervals, called epochs, using a pharmacokinetic model. The model is generally set by the device manufacturer; if a choice of multiple models is given, the operator must decide which one to use. The software requires entry of one or more patient parameters, such as age, height, and body weight. In practice, the system administers an initial bolus obtained by multiplying the target plasma concentration by the volume of the central compartment; it then administers the amount of drug needed to compensate for the drug leaving the central compartment by diffusion and elimination. TCI also offers the important advantage of being able to change the concentration initially set, such as increasing it if the intensity of the surgical stimulus becomes greater. In this case, the software takes into account the estimated amount of drug in the central compartment, administers as a bolus the amount missing to achieve the desired concentration, then reprograms the infusion rate. In case the target concentration is reduced, the infusion stops until the concentration in the central compartment reaches the set value.

Pharmacokinetic models are developed from data collected on a sample of individuals. They are therefore influenced by the characteristics of the subjects studied, usually healthy individuals, and the variables chosen by the investigator, for example, the decision whether or not to tie the calculation of central compartment volume to the patient's body size. It is therefore necessary to become aware of the limitations of the technique, particularly that actual anesthetic concentrations, which can be measured by analyzing plasma samples, may be significantly different from those estimated by the device. In clinical practice, therefore, it is always necessary to check whether the depth of anesthesia assessed with clinical and instrumental monitoring corresponds to the anesthetic concentration estimated by the TCI device and, if necessary, to vary the concentration set to deepen or superficialize the patient.

The variability of the pharmacokinetic models is easily appreciated by comparing the parameters of two of the most widely used models for propofol TCI, Marsh's and Schnider's (Table 1.2). In the former, the only individual variable is weight, which is involved in the calculation of the volume of the three compartments, while in the latter it is age, sex, body weight, and height that are involved in both the calculation of the volume of the compartments and that of the k constants. The volume of the central compartment predicted by Marsh's model is significantly greater than that predicted by Schnider's model, especially in subjects of larger body size. This difference results in the administration of a larger initial bolus (desired plasma

concentration multiplied by the volume of the central compartment) using this model; on the other hand, Schnider's model might be more suitable for induction of anesthesia in elderly or frail subjects, who exhibit increased sensitivity to the action of anesthetic. Minto's model for remifentanil is based on the patient's age and anthropometric parameters weight and height.

1.4.1 Effector Site

The time interval between the administration of an intravenous bolus of anesthetic and the maximum pharmacodynamic effect is called the time to peak effect (TTPE). This interval is independent of the magnitude of the bolus and is characteristic of each drug. Propofol has a value between 1.6 and 3.9 min; Table 1.3 shows the value for some opioids. TTPE represents the time required to reach equilibrium between the plasma concentration of the drug (central compartment) and that at the effector site, where the drug diffuses across the blood–brain membrane. Factors affecting its value include the drug's liposolubility and p*K*a, which affects the degree of dissociation at blood pH. During TTPE, the concentration in the central compartment decreases after the initial peak due to diffusion phenomena, while the concentration at the effector site increases because the anesthetic diffuses there from the central compartment. Therefore, the concentration at the effector site cannot match the peak maximum plasma concentration obtained immediately after the bolus.

During TCI, the plasma concentration of the anesthetic is kept constant because the infusion rate changes to compensate for diffusion and elimination phenomena. Under these conditions, the diffusion of the anesthetic into the effector site is expressed by an exponential equation characterized by the constant $k_{e,0}$; neither diffusion in the opposite direction, toward the central compartment, nor a volume of the effector site is contemplated in the pharmacokinetic models. The time required for the anesthetic concentration at the effector site to reach half the concentration in the central compartment ($t_{1/2\ ke0}$) expresses a concept similar to that of TTPE. Its value for propofol is 2.77 min, for midazolam 4 min, for remifentanil 1.4 min, for fentanyl 6.9 min, and for morphine 17.7 min. The software in the TCI devices allows the concentration at the effector site to be estimated and allows the operator to set this concentration instead of the plasma concentration. The advantage is a reduction in the latency of the anesthetic's effect, achieved by maintaining a higher plasma

Table 1.3 Time interval in minutes between the administration of an intravenous bolus of some opioids and maximum effect (time to peak effect, TTPE) [16, 17]

	TTPE (min)	p*K*a	Relative liposolubility
Remifentanil	1.4	7.1	50
Alfentanil	2.6	6.5	90
Fentanyl	3.2	8.4	580
Morphine	19	8.0	1

Values are influenced by the dissociation constant expressed by p*K*a and the liposolubility of the molecule

concentration for the time it takes to reach the desired concentration at the effector site level. Then, when the desired concentration has been reached, the infusion slows or stops for the time required for the two concentrations, in plasma and at the effector site, to equalize.

1.4.2 Anesthetic Half-Life and Recovery of Consciousness

The half-life of a drug ($t_{1/2}$) is equal to the time interval required for the plasma concentration to halve. This parameter is given by the ratio of the volume of distribution (Vd) to the clearance (Cl), which is the volume of plasma that is cleared of the drug in the unit of time. In the formula $t_{1/2} = 0.7 \times V\text{d}/\text{Cl}$, 0.7 represents the approximate value of the natural logarithm of 2. The volume of distribution is the ideal space in which the drug would be distributed at a given instant if it had everywhere a concentration equal to the plasma concentration (or to that of the central compartment in the pharmacokinetic model). During the phase in which the drug accumulates in peripheral tissues, the volume of distribution gradually increases and consequently the half-life rises. In practice, the half-life increases because at the end of the infusion not only does the central compartment have to be purified, but also the portion of the drug that has been transferred to the peripheral compartments has to be eliminated. However, the closer we get to achieving equilibrium between the compartments, the more the value of the half-life tends to stabilize.

The concept of context-sensitive half-life thus expresses the variability of drug half-life in relation to the duration of infusion and concerns the period of time from the start of administration to the achievement of equilibrium between pharmacokinetic compartments. In the case of intravenous anesthetics, the relatively short duration of administration (minutes or hours) makes the effects of drug distribution processes in the body particularly important. The context-sensitive half-life of a drug is represented on a graph as a function of infusion duration. For some drugs, such as sodium thiopental or fentanyl, the half-life increases markedly as the infusion is prolonged. For others, such as propofol, the increase is smaller and equilibrium is reached earlier. This is why the concept of context-sensitive half-life is important when conducting anesthesia with propofol, less so during prolonged sedation in the ICU. Remifentanil represents the edge case of a drug with a half-life that rapidly becomes context-insensitive because plasma concentration and half-life stabilize after only 12 min of a constant-rate infusion.

TCI systems offer an estimate of the time required for the patient to wake up by suspending the infusion at that time. The estimate is based on simulation of the plasma concentration decrease curve by zeroing out the external supply and considering only diffusion from the peripheral compartments and elimination through the excretory organs. It is thus possible to calculate the time required for the plasma concentration to fall below the threshold value needed to achieve hypnosis.

1.4.3 Drug Interactions

Intravenous anesthesia generally requires the administration of multiple drugs to achieve adequate levels of hypnosis and analgesia. Classically, a hypnotic and an opioid are combined. One of the advantages of this combination is the ability to reduce the dosages of both. Because of their pharmacokinetic characteristics that make them particularly manageable and their synergism, the drugs most commonly used for this purpose are propofol and remifentanil.

When associated, two drugs can be additive, synergistic, or antagonistic. They are additive when the doses needed by employing them in isolation can be halved by associating them. For example, abolition of the patient's response to surgical incision can be achieved with a TCI of propofol set at a concentration of 11 mcg/mL or with inhalation of sevoflurane at an end-expiratory concentration of 1.8 MAC. The same effect can be achieved by combining a TCI of propofol at 5.5 mcg/mL and inhalation of sevoflurane at an end-expiratory concentration of 0.9 MAC [18]. Two drugs are synergistic when the effect of their combination exceeds the sum of their individual effects. Propofol and remifentanil are an example of synergistic drugs. The patient's response to tracheal intubation can be abolished with a target plasma concentration of propofol of 10 mcg/mL or remifentanil of 10 ng/mL, but by associating the two drugs the required concentrations are 2 mcg/mL and 4 ng/mL [19]. Finally, two drugs are antagonists if their combination at half the dosage results in a lower effect than that of each drug given alone; examples of antagonist drugs are morphine and tramadol.

The synergistic effect between two drugs is graphically represented by a curve that relates the combinations of the two concentrations that achieve the desired effect. The concentrations may be in plasma or, better, at the effector site level, and the desired effect may be, for example, the absence of response to skin incision or tracheal intubation. The curve is a function of the percentage of subjects in whom the effect is achieved. It was shown earlier that the Cp50 of an intravenous anesthetic is the concentration sufficient to obtain the effect in 50% of cases. Synergy between two drugs is thus comprehensively described by a family of curves and is represented by a curvilinear surface within a three-dimensional graph in which the third axis is represented by the percentage of subjects in whom the effect is achieved [19].

1.5 Closed-Loop Anesthesia

Totally intravenous anesthesia is one of the fields of application of new technologies of using autonomous systems in anesthesia [20, 21]. In traditional anesthesia (open-loop), the anesthesiologist completes the circuit starting from the input of clinical parameters and data from monitoring systems, which describe the patient's status, with the effector system, that is, the anesthetic infusion pumps and their speed. The anesthesiologist then assesses the levels of anesthesia and analgesia and sets the drug infusion rate so as to keep the patient's parameters within the optimal range. A

TCI system facilitates the anesthesiologist's task because it independently compensates for the effects of drug delivery.

The closed-loop anesthesia technique autonomously links the monitoring system and the TCI (closed-loop) system. In this case, the anesthesiologist does not set a target anesthetic concentration, but a range of values for one or more measured parameters (e.g., Bispectral Index) and asks the system to keep those parameters within that range. The device software sets and varies the TCI system's target concentration to achieve the goal, changing the concentration as the monitored parameters change.

The potential benefits of a closed-loop system are many. Conceptually, the system optimizes the TCI because it corrects the inaccuracy of a general pharmacokinetic model applied to a particular patient based on the effects that are detected. In practice, numerous studies have shown that the ability of such systems to maintain benchmarks within the set range is superior to that of the human operator and that they often realize significant savings in drug consumption. In addition, the systems prevent over- and underdosing caused by inattention of the human operator or sudden changes in the intensity of the surgical stimulus, and can alert the anesthesiologist if abnormal circumstances occur, such as anesthetic consumption exceeding a limit value.

The limitations and potential risks of a closed-loop anesthesia system are partly related to the anomalies or inadequacy of the signal from the monitoring systems. For example, it is difficult to assess whether the depth of anesthesia is sufficient or excessive based on a single parameter. As a result, the initial one-input, one-output (SISO: Single Input, Single Output) systems have evolved into the multiple input, multiple output (MIMO: Multiple Input, Multiple Output) systems. Certainly, automated systems should not be regarded as devices that replace the anesthesiologist, but as supports that, similar to TCI systems, simplify the anesthesiologist's task [22].

1.6 Conclusions: Intravenous Anesthesia as Surfing

Many years ago, Talmage D. Egan and Steven L. Shafer, two authors who have made important contributions to the development of modern intravenous anesthesia, very effectively described the work performed by the anesthesiologist by resorting to the image of a surfer riding the crest of a wave [23].

The wave represents the curve that links the anesthetic concentration on the x-axis to its effects on the patient on the y-axis. The crest of the wave corresponds to the minimum concentration needed to achieve the required degree of hypnosis and/or analgesia. Increasing the concentration would unnecessarily expose the patient to the side effects of the drug; decreasing it would lead to too shallow anesthesia or insufficient analgesia. The anesthesiologist wants to stay on the crest of the wave to achieve the desired effects of the drug with the least risk of side effects. In addition, staying on the crest of the wave means having a rapid awakening of the patient at the end of the procedure because the decrease in plasma concentration immediately corresponds to a superficialization of the level of anesthesia. From

what has been said about the pharmacokinetics of intravenous anesthetics, staying on the crest of the wave is not easy, but to stay there, the anesthesiologist has three useful tools. Pharmacokinetics provides valuable information on reaching the crest of the wave, offering guidance on initial dosing based on patient size, age, and condition. Clinical and instrumental monitoring tells us whether we are actually at the crest of the wave or whether we need to administer additional doses to go up or temporarily stop dosing to go down. TCI systems are the third tool, which makes it easier for us to remain on the crest of the wave because they are very effective in stabilizing the drug concentration in the plasma or at the effector site. In manual adjustment, on the other hand, we have to assess the depth of anesthesia continuously and change the speed of the infusion pumps accordingly.

Alongside these three tools, Egan and Shafer posit a fourth, given by the availability of drugs such as propofol and remifentanil with pharmacokinetics particularly suited to TIVA. In fact, after only 15 min of a constant-rate intravenous infusion with no initial bolus, the plasma concentration of propofol reaches 80% of the concentration it will reach at steady state [24], and remifentanil 100% [25].

Table 1.4 reports some recommendations for safe practice of intravenous anesthesia issued by the Association of Anaesthetists and the Society for Intravenous Anaesthesia [26].

Table 1.4 Recommendations on the practice of intravenous anesthesia [26]

1.	All anesthesiologists should be trained and competent on TIVA. Schools of anesthesia should teach, train, and provide hands-on experience for anesthesia and critical care residents
2.	When general anesthesia is obtained with propofol, TCI should be used
3.	The initial concentration should be set based on the characteristics of the patient, other medications administered, and the clinical situation. Elderly and frail patients may benefit from a lower initial target concentration of propofol and subsequent adjustments
4.	Within an anesthesia department, it is preferable to use only one concentration of propofol and always dilute remifentanil to the same standard concentration
5.	The infusion set through which TIVA is delivered should have a Luer-lock connector at each end, an anti-siphon valve on the drug delivery line(s), and an anti-reflux valve on any infusion route. The route with the drug should join the others as close as possible to the point of entry into the vein to reduce dead space. The use of TCI-specific sets is recommended
6.	Infusion pumps should be programmed only after the syringe containing the drug has been placed
7.	The intravenous cannula or central venous catheter through which the infusion is delivered should, when possible, be visible during anesthesia
8.	Anesthesiologists should be familiar with the principles, interpretation, and limitations of EEG signal analysis. Direct observation of EEG tracing and muscle activity on electromyography can increase the usefulness of this type of monitoring
9.	EEG monitoring is strongly recommended when TIVA is associated with the use of muscle relaxants
10.	The standards of TIVA performance and monitoring adopted in the operating room should also be applied when TIVA is used in other environments

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