Total Intravenous Anesthesia Versus Inhalation Anesthesia: A Drug Delivery Perspective

Talmage D. Egan, MD

WHEN FORMULATING an anesthetic plan, the anesthesiologist deliberates over numerous therapeutic decisions. Perhaps chief among these is whether to proceed with an inhalation or intravenous anesthetic technique. Although there are many differences between the 2 approaches, they differ most fundamentally in terms of how the anesthesiologist gains access to the circulation for delivery of the anesthetic. This brief review aims to compare and contrast inhalation anesthesia with total intravenous anesthesia (TIVA) from a drug delivery perspective, making the case that advances in TIVA drugs, clinical pharmacology concepts, technologies, and techniques over the last 25 years have transformed TIVA into an attractive alternative to more traditional inhalation anesthesia methods.

DRUG DELIVERY: INHALATION VERSUS TIVA

Administering volatile anesthetics through the lung via a calibrated vaporizer affords several fundamental advantages compared with intravenous delivery as summarized in the upper panel of Figure 1.[1] These advantages are primarily a function of gaining access to the circulation indirectly through the lung. Because uptake of inhaled anesthetic progressively diminishes as equilibrium between alveolar and pulmonary capillary partial pressures is approached, the vaporizer setting is a proportional reflection of the anesthetic concentration in the blood and therefore at the site of drug action at steady state. This enables accurate administration of the inhaled drug to a target concentration; the anesthesiologist can set an upper limit above which the partial pressure cannot rise. Moreover, the expired concentration of the inhaled agent can be measured and confirmed by respiratory gas monitoring, ensuring that the targeted concentration has been achieved (pharmacokinetic [PK] exactness). Finally, the pharmacodynamic (PD) significance of the measured concentration is standardized in terms of minimum alveolar concentration (MAC), a well-developed and widely understood concept, which provides an increased degree of PD exactness.

As summarized in the lower panel of Figure 1, at the beginning of the TIVA era, intravenous anesthesia techniques were associated with significant disadvantages compared with inhalation anesthesia.[1] When access to the circulation for drug delivery is obtained directly as with all intravenous techniques, there is nothing to prevent indefinite uptake of the drug (ie, there is no equilibration process as with inhalation drug delivery). Therefore, without the aid of a PK model, the infusion rate of an intravenous anesthetic does not reveal much about the temporal profile of drug concentration in the blood, preventing administration targeted to a designated concentration. Moreover, there was not a method to measure continually the concentration of intravenous anesthetics in real time, preventing equivalent PK exactness. Finally, at the dawn of the TIVA era, concentration-effect relationships analogous to minimum alveolar concentration for intravenous anesthetics had not yet been firmly established, hindering the achievement of equivalent PD exactness compared with inhalation anesthesia.

Intravenous anesthesia research over the last 25 years has focused on mitigating these shortcomings identified in the early days of TIVA practice. Because the fundamental advantage of inhalation anesthesia (ie, the equilibration process that occurs when gaining access to the circulation via the lung) is obviously not applicable to intravenous techniques, the disadvantages of TIVA stemming from this difference in access to the circulation must be addressed in other ways. As summarized in Table 1, TIVA advances have focused on achieving enhanced drug delivery and improved PK and PD exactness.[2] These advances have come in the form of new drugs, delivery technologies, and clinical pharmacology concepts.

NEW DRUGS: PROPOFOL AND REMIFENTANIL

From a practical perspective, to gain traction over inhalation anesthesia techniques, TIVA practice required anesthetic agents with certain qualities. Perhaps most importantly, the drugs needed to be sufficiently short acting so that recovery could be achieved reasonably quickly despite long infusions. Some PD advantages of TIVA compared with inhalation agents, such as less nausea, would also make TIVA attractive.

The advent of propofol ushered in the TIVA era. Propofol has PK and PD properties that are well suited to the implementation of a TIVA paradigm. The reasonably rapid decline in concentration despite long infusions[3] and the clear-headed, often nausea-free recovery contributed to making

From the Departments of Anesthesiology, Pharmaceutics, and Bioengineering, University of Utah School of Medicine, Salt Lake City, Utah.

Address reprint requests to Talmage D. Egan, MD, University of Utah School of Medicine, Departments of Anesthesiology, Pharmaceutics, and Bioengineering, 50 N. Medical Drive, Salt Lake City, Utah 84132. E-mail: Talmage.Egan@hsc.utah.edu

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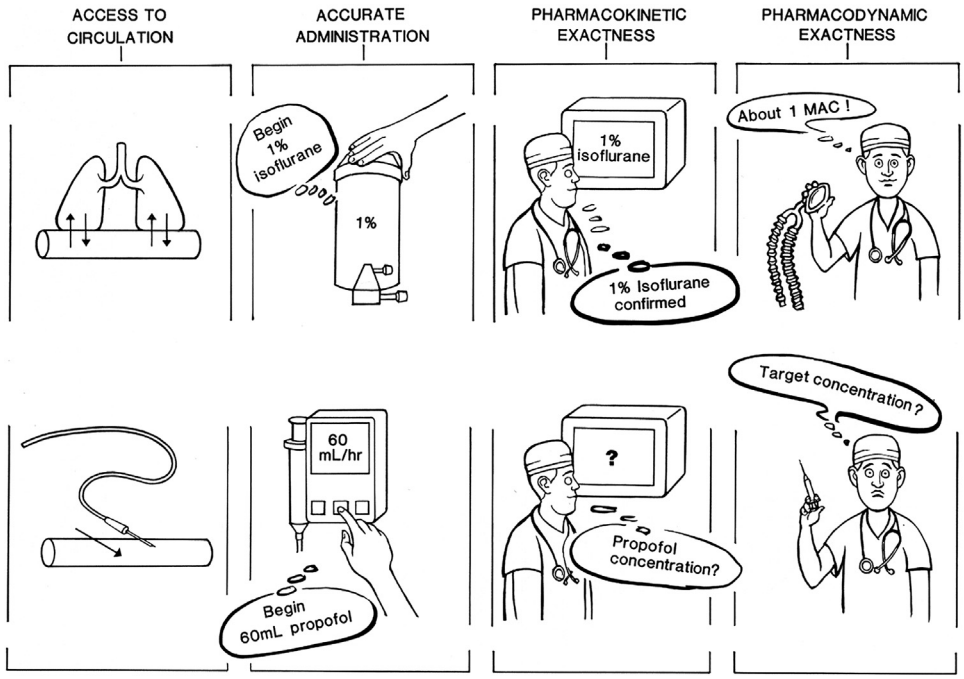

Fig 1. A comparison of anesthetic delivery by inhalation (upper panel) or intravenous infusion (lower panel) at the beginning of the TIVA era. Inhalational anesthetic delivery benefits from the fundamental advantage of gaining access to the circulation indirectly. The equilibration process that takes place across the lung vasculature enables drug delivery to well defined anesthetic targets (ie, MAC) in the concentration domain using a calibrated vaporizer. See text for detailed explanation. TIVA, total intravenous anesthesia; MAC, minimum alveolar concentration. Adapted with permission.[1]

propofol the pharmacologic foundation of TIVA practice.[4–7] Prior to propofol's availability, the existing sedative-hypnotic agents were either active too long (eg, sodium thiopental) or were associated with unacceptable adverse effects with prolonged administration (eg, etomidate).

Remifentanil, an esterase-metabolized opioid, was designed with the priorities of a modern, often outpatient, anesthesia practice in mind. Utilizing a "soft-drug" paradigm wherein the drug is designed to be metabolically labile and thus have a very high clearance,[8] remifentanil's effects dissipate quickly after an infusion is terminated.[9] The high clearance is also the kinetic attribute partly responsible for the rapid achievement of a steady state after beginning a remifentanil infusion; that is, both the "front-end" and "back-end" kinetics of remifentanil are well suited to the establishment, maintenance, and recovery from TIVA.[10] Given these pharmacologic properties, remifentanil is frequently combined with propofol for the provision of TIVA.

The pharmaceutical industry, in collaboration with clinical experts, is actively developing a variety of new agents that may enhance TIVA practice in the future.[11] Capitalizing on the advantages of the "soft-drug" approach applied to anesthesia, these research efforts are in large part focused on esterase-metabolized benzodiazepines (eg, remimazolam) and other sedative hypnotics (eg, etomidate and propanidid analogues).[12–14] Novel propofol formulations, typically in nonlipid excipients, are also an area of active interest.[15]

Table 1. Advances in TIVA Addressing Disadvantages Compared to Inhalation Anesthesia Categorized According to the Paradigm Introduced in Figure 1

Access to the Circulation
None
Accurate Administration
Target controlled infusion
Clinical pharmacology guidance systems
Pharmacokinetic/Pharmacodynamic Exactness
Kinetically responsive drugs (eg, propofol, remifentanil, and other "soft drugs" in development)
Measurement of propofol in expired gas (ie, "end-tidal" propofol)
Advanced kinetic concepts (eg, CSHT)
Advanced dynamic concepts (eg, response-surface drug interactions, the effect-site)

Abbreviations: CSHT, context-sensitive half-time; TIVA, total intravenous anesthesia.

ADVANCES IN DRUG DELIVERY: TARGET-CONTROLLED INFUSION, ADVISORY SYSTEMS, AND EXPIRED PROPOFOL

Enabling drug administration in the concentration domain was an obvious early goal of intravenous anesthesia research efforts. By coding a PK model into a computer program and linking it to an electronic pump, delivery according to a drug's specific kinetic profile was achieved.[16] This concept was first applied to propofol[17]; commercial embodiments of the idea are now available for many commonly used intravenous anesthetics (although sadly not in the United States).[18] Called target-controlled infusion (TCI) systems, the user of a TCI system designates a target concentration to achieve, rather than specifying an infusion rate as with a traditional calculator pump. Using a PK-model-based BET (bolus, elimination, and transfer) algorithm, the TCI system calculates the necessary