Total Intravenous Anesthesia: A Primer

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Background and Advantages

Total Intravenous Anesthesia (TIVA) is an increasingly common anesthesia technique. It is an alternative to the use of inhalational anesthetics, and has advantages that can be useful in certain situations. TIVA is portable, non-polluting, and does not require bulky gas delivery systems or waste anesthesia gas connections. It functions well even without an endotracheal tube or supraglottic airway in place. This can happen during a rigid bronchoscopy, for instance.

Additionally, some TIVA medication combinations are associated with high clarity on emergence and low incidence of postoperative nausea and vomiting (PONV), which is desirable for outpatient anesthetics. More than a century ago (1911) it was reported with intravenous administration of diethyl ether(!) that "the patient begins to come round

very soon after the anaesthetic is stopped and is able to converse rationally within a few minutes"[1]. Moreover, it was noted that "post-anaesthetic vomiting and pulmonary irritation are both of them extremely rare". Hence, the low PONV rate observed with modern TIVA medications is not a new finding.

Still more potential benefits of TIVA include reducing the recurrence rates of some types of malignancies (compared to volatile anesthetics), and general anti-inflammatory effects.

TIVA is usually done with a propofol infusion as a core component. Additional medications, such as opioids and/or ketamine, are often added to achieve a desired objective. Additionally, medications such as dexmedetomidine, ketamine (in lower doses), lidocaine, and magnesium are sometimes added as an adjunct.

TIVA Pharmacokinetics and Pharmacodynamics

Volatile anesthetic concentrations are easily measured with a gas analyzer and displayed as an end-tidal anesthetic concentration that reflects the concentration in the lungs. The TIVA analogue is plasma concentrations of the various medications. Unlike a gas analyzer, there is no continuous monitor for TIVA medication concentrations, and any blood samples drawn would likely have a very long turnaround and thus not clinically useful. Exhaled propofol analysis is in the research stage and appears promising, but there are currently no commercial products available for monitoring propofol plasma concentrations in real-time. Instead, clinicians need to estimate plasma concentrations and make changes up or down without patient-specific data. Fortunately, the use of pharmacokinetic mathematical models allows reasonable accuracy. The United States is the only country without computer-controlled TIVA based on pharmacokinetic models; American clinicians must use heuristics instead.

Minimum Alveolar Concentration (MAC) is a statistic for inhalational anesthetics defined as the concentration at which 50% of patients don't respond to surgical stimulation. The equivalent for TIVA is called EC50. Like MAC, the probability of responding to surgical stimulation rapidly decreases with incremental increases in plasma concentration beyond the EC50.

The EC50 of propofol has been measured at over 8 mcg/mL.[2] This is a very high plasma concentration that would require a high-dose infusion to maintain, and would experience a prolonged emergence, since the time required for the plasma concentration to become low enough to be awake would be significant. And keep in mind at this concentration 50% of patients will move to surgical stimulation, which necessitates an even higher plasma concentration if immobility is the objective.

Propofol's inefficiencies at inhibiting movement would be a significant problem for TIVA if it were not for the fact that additional medications interact favorably with propofol. Opioids, for instance, are synergistic with propofol. This means that the combination of propofol and an opioid allows a desired effect at lower plasma concentrations than either medication alone could achieve. Figure 1 shows the EC50 for various combinations of propofol and the opioid alfentanil; the concavity of the curve indicates that proportionately less propofol and alfentanil are required when used together (synergy). This property illustrates a secret to effective TIVA: **Well-selected medications should be co-administered with propofol**, and this synergy exploited for the entire case. At the end, when both medications are discontinued, the plasma concentrations of each medication eventually reach a point where the synergy collapses and is no longer able to maintain general anesthesia; this represents emergence from anesthesia.

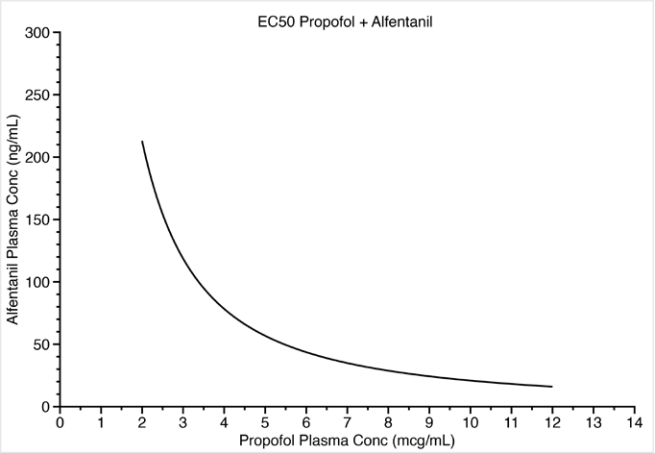

Figure 1: *The EC50 for various combinations of propofol and the opioid alfentanil*

Remifentanil is an ultra-short-acting opioid (typical half-life is under 5 minutes) that is frequently co-administered with propofol for TIVA. The combination inhibits movement and breathing and is associated with a rapid and clear emergence. The presence of remifentanil drastically decreases the EC50 of propofol to about 2.5 mcg/mL [3], allowing for the fast emergence.

- Bolus: 1 mg/kg
- Infusion scheme:
  - 167 mcg/kg/min x 10 mins
  - 133 mcg/kg/min x 10 mins
  - 100 mcg/kg/min thereafter

} Achieves plasma concentration ≈3-4 mcg/mL

"Bristol Technique" for Propofol Administration

American clinicians lack computer-controlled infusions and must consequently rely on pharmacokinetic heuristics to achieve the approximate plasma concentration. For the typical propofol plasma target when remifentanil is also used (2.5 - 4 mcg/mL), the heuristic known as the "Bristol Technique" or the "10-8-6 rule" can be employed. It consists of a loading dose of 1 mg/kg, followed by an infusion of 10 mg/kg/hr (167 mcg/kg/min) for 10 minutes, then 8 mg/kg/hr (133 mcg/kg/min) for another 10 mins, and then 6 mg/kg/hr (100 mcg/kg/min) thereafter.[4] This generally achieves plasma concentrations in the range of 3-4 mcg/mL. (Pediatric patients require higher dosing schemes to get to the same plasma concentrations. One such published scheme is the McFarlan dosing scheme.[5] This article, however, is targeted to adult patients.) The Bristol Technique illustrates an aspect of propofol pharmacokinetics: **Propofol needs to be loaded**, with initially higher, then somewhat lower infusion rates to first achieve and subsequently maintain a stable plasma concentration.

Remifentanil, with its very short duration of action, can be run at high doses and still emerge quickly, because it is rapidly metabolized. This enables the propofol to be run lower. Remifentanil achieves a new steady-state plasma concentration in approximately 20 minutes on an infusion, which is incredibly fast compared to most medications. Other medications, such as sufentanil or ketamine, can't be run as high and still wake up quickly. Thus, the optimal propofol plasma concentrations are higher when combined with these medications

See Table 1 for more information on TIVA mixtures and some infusion schemes based on population averages. There is a large inter-person variability in the response to each medication and the degree of synergy between the medications. Additionally, these population-average plasma targets from the literature are largely derived from Dutch gynecology patients, and might not translate perfectly to all scenarios. Consequently, depth of anesthesia monitoring is recommended to titrate to each individual patient.

Mixture	Use	Plasma Targets	Recipe
Propofol + Remifentanil	Clarity on emergence, immobility, apnea	**Propofol:** 2.5-3.5 mcg/mL **Remifentanil:** 6-9 ng/mL	**Propofol:** • 1 mg/kg bolus • 150-175 mcg/kg/min x 10mins • 120-140 mcg/kg/min x 10 mins • 100 mcg/kg/min for next 3+ hrs **Remifentanil:** 1-3 mcg/kg bolus, then 0.05-0.25 mcg/kg/min (ideal body weight)
Propofol + Ketamine	Spontaneous breathing, hemodynamic stability	**Propofol:** 4-5 mcg/mL **Ketamine:** ≈300 ng/mL	**Propofol:** • 2 mg/kg bolus • 175 mcg/kg/min x45 mins • 150 mcg/kg/min **Ketamine:** • 0.75 mg/kg bolus • 1 mg/kg/hr infusion
Propofol + Sufentanil	TIVA with lingering opioid analgesia	**Propofol:** 4-4.5 mcg/mL **Sufentanil:** 0.2-0.3 ng/mL	**Propofol:** • 2-2.5 mg/kg bolus • 200 mcg/kg/min x45 mins • 170 mcg/kg/min • May decrease to 140 mcg/kg/min at hour 3. **Sufentanil:** • 0.25 mcg/kg bolus • 0.2-0.3 mcg/kg/hr infusion

Table 1: *TIVA mixtures and some infusion schemes based on population averages*

Elderly patients will obtain higher plasma concentrations for a given infusion scheme, and at the same time require lower concentrations to achieve the same effect. This implies that dosing may need to be dramatically lowered in the elderly. Again, depth of anesthesia monitoring can be beneficial here.

TIVA Medication Combinations

In addition to propofol-remifentanil TIVA, there are other combinations that are sometimes employed. Propofol and sufentanil infusions are good for patients in whom some lingering opioid postoperatively is desired. Large spine surgeries, which are often done on patients with chronic pain who take high doses of opioids preoperatively, are good examples of cases appropriate for propofol and sufentanil.

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Propofol and ketamine is another classic combination. Unlike the propofol-opioid combinations, this results in good spontaneous breathing and hemodynamic stability. It is also

helpful in opioid-tolerant patients, as ketamine produces analgesia through mechanisms besides opioid receptors. Unlike many medications often used with propofol, such as lidocaine and remifentanil, ketamine is stable when physically mixed with propofol, and can be added to a bottle of propofol for a single-infusion solution.

Ketamine is also useful as an adjunct (in lower infusion rates) with a propofol-opioid anesthetic for patients with chronic pain or depression, or to blunt hyperalgesia that can develop from administration of opioids. Dexmedetomidine may share some of these benefits when used as an adjunct.

Engineering for High Reliability Infusions

Unlike volatile anesthetics, which utilize the breathing circuit as a conduit for administration, intravenous infusions lack disconnect alarms and gas analyzers. It is, therefore, important to optimize the intravenous tubing to minimize the chance of accidental disconnection or retrograde flow up the IV fluid bag. The includes ensuring tight connections in the IV lines and confidence that the IV works well.

Well-designed infusion tubing has built-in one-way valves and low dead space. The valves prevent other medication and fluid boluses from backing up the infusion pumps. They also prevent the TIVA infusions from coming up into the IV fluid line. This helps to maximize the probability that the infusions will continuously flow into the vein. Additionally, the low dead space seen by the infusions makes them more responsive (changes in infusion rates more quickly get to the patient), as well as having less medication in the IV tubing that gets surged into the patient when administering another medication or increasing the IV fluid flow rate. International TIVA guidelines recommend the use of infusion tubing with these characteristics.

Depth of Anesthesia Monitoring with TIVA

Depth of anesthesia monitoring, such as with BIS™ is recommended with TIVA. Multiple studies demonstrate reduced incidence of accidental awareness under anesthesia using depth of anesthesia monitoring with TIVA. Unlike inhalational anesthetics, which can confirm medication delivery with a breathing circuit gas analyzer, TIVA presently has no analogous monitor. Thus, depth of anesthesia monitoring is especially useful.

Perhaps even more important, however, is the use of depth of anesthesia monitor for avoiding the other end of the spectrum: excessively deep anesthesia. This can save anesthesia medication cost, reduce the time to emergence, and potentially modulate longer-term outcomes.

Conclusion

TIVA is increasingly becoming a routine part of an anesthesia clinician's toolkit. It has several potential advantages that can be exploited if done properly. Availability of appropriately designed tubing and infusion pumps, as well as depth of anesthesia monitors, is important for the safe and efficient delivery of this very useful technique.

Take the QUIZ On The Next Page

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Continuing Education Quiz

To test your knowledge on this issue's article, provide correct answers to the following questions on the form below. Follow the instructions carefully.

1. Which of the following is an advantage of TIVA?
A. Ease of monitoring plasma concentrations
B. Lower risk of postoperative nausea and vomiting (PONV)
C. No requirement for continuous IV access
D. Can be turned on and off with no setup

2. Which is true regarding quickly establishing and maintaining a constant propofol plasma concentration?
A. Propofol cannot be bolused
B. It requires initially lower, then gradually increasing infusion rates
C. The infusion rate cannot vary over time
D. It requires initially higher, then gradually decreasing infusion rates

3. Which TIVA medication or combination of medications would be most appropriate for an anesthetic goal of clarity on emergence, immobility during the procedure, and no spontaneous breathing attempts?
A. Propofol only
B. Propofol and ketamine
C. Propofol and remifentanil
D. Propofol and dexmedetomidine

4. What technique allows for running at a lower propofol plasma concentration than would be otherwise required?
A. Use of synergistic medications with propofol
B. Avoidance of opioids
C. Using a gas analyzer
D. Increasing the dead space in the IV tubing

5. How do TIVA medications affect elderly patients (compared to their younger counterparts)?
A. Elderly are less sensitive to the effects of TIVA medications
B. Elderly patients generally achieve lower plasma concentrations for a given infusion scheme than younger patients
C. Depth of anesthesia monitoring is not helpful in elderly patients with TIVA
D. Elderly patients get higher plasma concentrations for a given infusion scheme compared to younger patients

6. When was TIVA first described?
A. 1968
B. Late 1970's
C. Early 1990's
D. More than a century ago

7. What is a specific benefit of using IV tubing with low dead space?
A. There is no need for one-way valves
B. Medication infusion changes are more responsive
C. A high carrier fluid rate is required
D. Larger IV catheters can be used

8. Which of the following equipment is needed for TIVA?
A. Infusion pumps and a reliable IV
B. A gas analyzer that displays MAC values
C. An endotracheal tube or supraglottic airway (such as LMA)
D. Scavenging / waste anesthesia gas connection

9. What would be the most appropriate choice of TIVA medication(s) for hemodynamic stability and spontaneous breathing?
A. Propofol only
B. Propofol and sufentanil
C. Propofol and remifentanil
D. Propofol and ketamine

10. Which is true regarding the use of ketamine in TIVA?
A. Ketamine is contraindicated in patients with depression
B. Ketamine is useful in patients with chronic pain and/or opioid tolerance
C. Ketamine cannot be mixed with propofol
D. Propofol and ketamine together result in a large drop in blood pressure

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3: A B C D	**8:** A B C D
4: A B C D	**9:** A B C D
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