Total Intravenous Anesthesia: Theoretical Foundation and Practical Considerations

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Disclosures

In the last 2 years, Dr. Egan has the following industry relationships to disclose:

- Founder and equity partner: Medvis
- Research support: Medtronic
- Scientific Advisory Board Member: Acacia Pharma
(Brief introduction to TIVA theory and practice...)
Overall Goal

Establish the scientific and practical foundation upon which to base a TIVA practice.
University of Utah Department of Anesthesiology
General Anesthetic Technique
(May 2014–June 2022)

TIVA 152,215 (53%)
Volatile 134,714 (47%)
Gaining access to the circulation via the lung affords fundamental advantages that have set a standard for innovation in TIVA practice since the mid 1990s.
Drug Delivery: TIVA vs. Inhaled (Circa 1990s)

Access to Circulation

Accurate Administration

Pharmacokinetic Exactness

Pharmacodynamic Exactness

- Begin 1% isoflurane
- 1% isoflurane confirmed
- About 1 MAC!
Drug Delivery: TIVA vs. Inhaled (Circa 1990s)

Access to Circulation

Accurate Administration

Pharmacokinetic Exactness

Pharmacodynamic Exactness

- Begin 1% isoflurane
- 1% isoflurane confirmed.
- About 1 MAC!

- Begin 60 mL/hr propofol
- Propofol concentration?
- Target concentration?

Egan (J Clin Anesth 1996)
Anesthesia posology (the study of drug dosing) is fundamentally different than other specialties of medicine.
Getting the dose right: anaesthetic drug delivery and the posological sweet spot

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Posology, a scientific term not in common usage, is the science of drug dosage; it is thus a branch of clinical pharmacology (or perhaps a synonym of sorts). Combining the Greek words ‘posos’ (how much) and ‘logos’ (science), posology can be thought of more simply as ‘dosology’. In the posology of anaesthesia, the fundamental question anaesthetists must answer each day is, ‘What is the right anaesthetic dosing strategy for my patient?’

In this issue of the British Journal of Anaesthesia, van den Berghe and colleagues report a novel approach to optimizing perioperative management in anaesthesia. Their study was an attempt to personalize target-controlled infusion (TCI) therapy with a single observation from the patient. Taking a Bayesian approach, the authors started with pharmacokinetic (PK) parameters from a population model and then adjusted them based on the difference between what the patient actually received and what was predicted. This gives the adjusted model the empirical weight of the observation, normalized by their variability. This moves the adjusted system from the a priori starting point

“Combining the Greek words ‘posos’ (how much) and ‘logos’ (science), posology can be thought of more simply as ‘dosology’.”
General Approach to Anesthesia Posology

Egan (Anesth Analg 2018)
Posology in Anesthesia: A Venn Diagram

Most Therapeutic Areas

Effective  Safe

High Therapeutic Index

Kuck & Egan (Br J Anaesth 2017)
Posology in Anesthesia: A Venn Diagram

Most Therapeutic Areas

Effective
Safe
High Therapeutic Index

Anesthesia Therapeutics

Efficient
Anesthesia posology is optimized here.
Effective
Safe
Low Therapeutic Index

Kuck & Egan (Br J Anaesth 2017)
A surfing analogy is helpful in understanding the modern approach to anesthesia posology.
Posology in Anesthesia: A Surfing Analogy

Egan & Shafer (Anesthesiology 2003)
Posology in Anesthesia: A Surfing Analogy

- **Ego & Shafer (Anesthesiology 2003)**
Posology in Anesthesia: A Surfing Analogy

Egan & Shafer (Anesthesiology 2003)
Posology in Anesthesia: A Surfing Analogy

Egan & Shafer (Anesthesiology 2003)
Posology in Anesthesia: A Surfing Analogy

- **Emax**: Dynamic
- **Pharmaceutic**: Kinetic
- **Low**, **EC50**, **High**

Egan & Shafer (Anesthesiology 2003)
There are three TIVA practice domains (i.e., dose, concentration, & effect). The effect domain is optimal.
Three TIVA Practice Domains

- **Manual Control**
  - Dose
  - Calculator Pump
  - Standard Monitor

- **Open Loop Control**
  - Concentration
  - Target Controlled Pump
  - Standard Monitor
  - Pharmacokinetic Simulation

- **Closed Loop Control**
  - Effect
  - Effect Controlled Pump
  - Standard Monitor
  - Pharmacokinetic Simulation
  - Effect Monitor

Prior Knowledge of Dose, Concentration, and Effect:
- Setting/Adjusting Dose, Concentration, or Effect

Electronic Feedback:
- Clinical Feedback

Effect Sensor:
- Electronic Feedback

Drug Infusion:
- Effect Monitor

Egan (Anesth Analg 2018)
The Dose Domain

- Simple to use
- Familiar to all

- Ignores temporal changes
- Slow to steady-state
- Ignores intersubject variability

Egan (Anesth Analg 2018)
The Concentration

+ Automates dosage calculations
+ Accounts for temporal changes
+ Quick to steady-state
+ Accounts for co-variante effects (PK)

- Ignores intersubject variability
- Less familiar (USA)

Egan (Anesth Analg 2018)
The Effect Domain

- Automates dosage calculations
- Accounts for temporal changes
- Quick to steady-state
- Accounts for co-variate effects (PKPD)
- Accounts for intersubject variability

- Complicated control system (automated)
- Suboptimal sensors
- Less familiar
- Unintended consequences?

Closed Loop Control (or Open Loop)

Usually Best!

Most important!

Egan (Anesth Analg 2018)
Certain pharmacokinetic attributes inform TIVA posology for bolus and infusions conditions. These attributes are best understood through PK-PD simulation.
Clinical Inference via PK/PD Simulation

Dose of Interest → PK-PD Simulation → PK/PD Prediction

Simulations

Cp
Ce

Effect

Time
Surprisingly long for most anesthetic drugs...
Infusion Back-End

What amount of decrease is required? How long will it take?

- Time to 50% decrease
- Time to 75% decrease
- Steady State
- Infusion Stops

% Peak Cc

Time (min)
A given decrement almost always takes longer with longer infusions...
Impact of Infusion Duration

75% Decrement Times

Longer and longer...
Certain pharmacodynamic concepts inform TIVA posology. Chief among these are propofol-opioid pharmacodynamic interactions.
MAC Reduction by Opioids

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
Propofol $C_{p50}$ Reduction by Opioids

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
Propofol-Opioid PD Interaction

1. Opioids reduce $Cp_{50}$ synergistically.

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
Propofol-Opioid PD Interaction

Cp₅₀ reduction is substantial (75%+).
Propofol-Opioid PD Interaction

Most \( C_{p50} \) reduction occurs at moderate opioid levels.
Propofol-Opioid PD Interaction

Cp₅₀ reduction is not complete.

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
5 An infinite number of hypnotic-opioid combinations achieve $C_{p50}$. 

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
Propofol-Opioid PD Interaction

Propofol-Opioid Optimal Ratio?
Propofol-Opioid PD Interaction

1. Opioids reduce $Cp_{50}$ synergistically.
2. $Cp_{50}$ reduction is substantial (75%+).
3. Most $Cp_{50}$ reduction occurs at moderate opioid levels.
4. $Cp_{50}$ reduction is not complete.
5. An infinite number of hypnotic-opioid combinations achieve $Cp_{50}$.

Ogura & Egan (in Hemmings & Egan, Elsevier 2019)
Simulation of propofol’s pharmacokinetic behavior helps inform posological decisions in TIVA.
Bolus Front-End & Back-End

50-year-old, 75 kg, 175 cm male

Rapid onset, moderately rapid offset (depends on dose)...
Concentrations rise throughout the course of a typical length case...

Infusion Begins (100 mcg/kg/min)
Induction bolus produces “supratherapeutic” concentrations for a time, then gradual rise begins…

**Impact of Loading Dose**

- Propofol Ce (mcg/ml)
- **Bolus (150 mg) & (100 mcg/kg/min) Infusion**
- Time (min)
Infusion Back-End

Target Controlled Infusion!

Back-end behavior changes as the infusion goes on...

75% Decrement

Propofol Ce (mcg/ml)

Infusion Duration (min)
Impact of Infusion Duration

Standard Infusion!

Back-end behavior slightly different for standard infusions (i.e., not at steady-state)...

Propofol C<sub>e</sub> (mcg/ml)

Bolus (50 mg)
Infusion (100 mcg/kg/min)

Awake C<sub>e</sub>

Time (min)
Context Sensitive Half-Time

Context sensitive half-time assumes TCI administration...

- Thiopental
- Midazolam
- Ketamine
- Propofol
- Etomidate

Infusion Duration (hours)

Context Sensitive Half-Time (min)

Obara & Egan (in Hemmings & Egan, Elsevier 2019)
Simulation of remifentanil and fentanyl pharmacokinetic behavior helps inform posological decisions in TIVA.
Fentanyl slower peak, much slower offset...

Normalized to peak Ce!
Remifentanil reaches steady-state rapidly; fentanyl does not reach steady-state...
Remifentanil levels rapidly decline...
Remifentanil is the only TIVA drug with a time independent context sensitive half-time...
The clinical state changes quite a bit with these fentanyl fluctuations…
Disruptive Impact of Boluses

Propofol (mcg/ml)

Cp\textsubscript{90}

“Sweet Spot”

Cp\textsubscript{50}

Opioid (xg/ml)
Disruptive Impact of Boluses

- **Cp90**
- **Cp50**
- "Sweet Spot"

Propofol (mcg/ml) vs. Opioid (xg/ml)
Transition Opioid

Remifentanil Infusion (0.15 mcg/kg/min)

Remifentanil

Remifentanil Infusion Off

Time (min)
Transition Opioid

Remifentanil Infusion (0.15 mcg/kg/min)

Remifentanil

Remifentanil Infusion Off

Fentanyl

Fentanyl Bolus (50 mcg)

PACU

Time (min)

% Peak Ce

30 45 60 75 90 105
Certain practical tips are helpful for successful TIVA practice.
Be Alert for Infusion Disruption

IV Flowing

IV Kinked, Not Flowing
Check for Pump Programming Error

Typical Rate = 10-20 ml/Hr

Typical Rate = 40-60 ml/Hr
Consider Using EEG

EEG waveform is reassuring!

Raw and Processed EEG

Effect Sensor

Propofol 100 mcg/kg/min 50 ml/Hr
Check Infusions Frequently

Time to check infusion!

5 Min

Propofol
100 mcg/kg/min
50 ml/Hr

TAKE 5 FOR TIVA
Consider Real Time PK/PD Simulation

Simulation suggests time to stop infusion.

Pharmacokinetic Simulation

Remifentanil
0.2 mcg/kg/min
15 mL/Hr
Adjust Dose for Senior Patients

Older patients will require lower doses.

Pharmacokinetic Simulation

Propofol 100 mcg/kg/min  50 ml/Hr
Impact of Age

Obara & Egan (in Hemmings & Egan, Elsevier 2019)
Adjust Pump Weight Setting for Obese Patients

Pump weight setting needs adjustment for obese patient.
Impact of Body Weight

Remifentanil Ce (ng/ml)

70 kg patient
Typical Target Ce
175 kg patient

Bolus (75 mcg) & Infusion (15 mcg/min)

Time (min)

Obara & Egan (in Hemmings & Egan, Elsevier 2019)
Deepen Anesthesia with Small Bolus and Infusion Rate Increase

Need to deepen anesthesia!

Standard Monitor

Propofol
100 mg/kg/min
50 ml/Hr

Effect Sensor

TAKE 5 FOR TIVA
Impact of Bolus & Infusion

- Bolus (100 mg) & Infusion (100 mcg/kg/min)
- Signs of Inadequate Anesthesia
- Infusion Rate Increase to (125 mcg/kg/min)
Impact of Bolus & Infusion

- **Bolus (100 mg) & Infusion (100 mcg/kg/min)**: Initial propofol concentration rising rapidly.
- **Bolus (20 mg) & Infusion Rate Increase (125 mcg/kg/min)**: Propofol concentration stabilizes for a period, then increases after 30 minutes due to bolus injection and adjustment of infusion rate.
- **Signs of Inadequate Anesthesia**: Indicates the need for additional bolus or increased infusion rate to achieve adequate anesthesia level.
Supplementary Material
Target Controlled Infusion System

Pharmacokinetic Model

Pump Control Algorithm

Calculated Infusion Rate

Varying Rate

Pump

Drug Infusion

Patient

C-predicted

Assessment of Patient Response

Knowledge of “Therapeutic Windows”

Physician

Set Target

5 ng/mL

Egan (Anesthesiology 2003)
Target Controlled Infusion Practice

Prior knowledge:
- Pharmacologic models
- Therapeutic windows
- Covariate effects

Current knowledge:
- Real-time assessment

To operate:
- Select pharmacokinetic model
- Input covariates
- Choose effect-site or plasma control
- Designate/adjust target concentration

TCI is the most sophisticated titration...

Egan et al (Br J Anaesth 2020)