Total Intravenous Anesthesia: Theoretical Foundation and Practical Considerations

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University of Utah School of Medicine

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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

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MPOG
MULTICENTER PERIOPERATIVE OUTCOMES GROUP

THRIVE

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(Brief introduction to TIVA theory and practice…)

Outline

- TIVA vs Inhaled Anesthesia from a Drug Delivery Perspective
- Posological Considerations in TIVA
  - A Venn diagram
  - A surfing analogy
  - 3 practice domains
- ~~Pharmacokinetic/Dynamic Models and Simulation Applied to TIVA~~
- "Must Know" Pharmacokinetic/Dynamic Attributes of TIVA Drugs
- Propofol & Opioid Kinetics and TIVA
- Tips and Tricks for TIVA

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Overall Goal

Establish the scientific and practical foundation upon which to base a TIVA practice.

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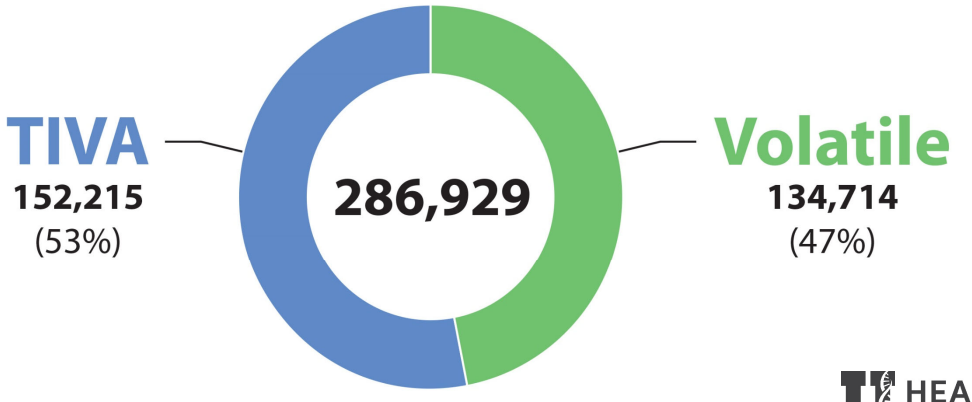
University of Utah Department of Anesthesiology
General Anesthetic Technique
(May 2014–June 2022)



HEALTH
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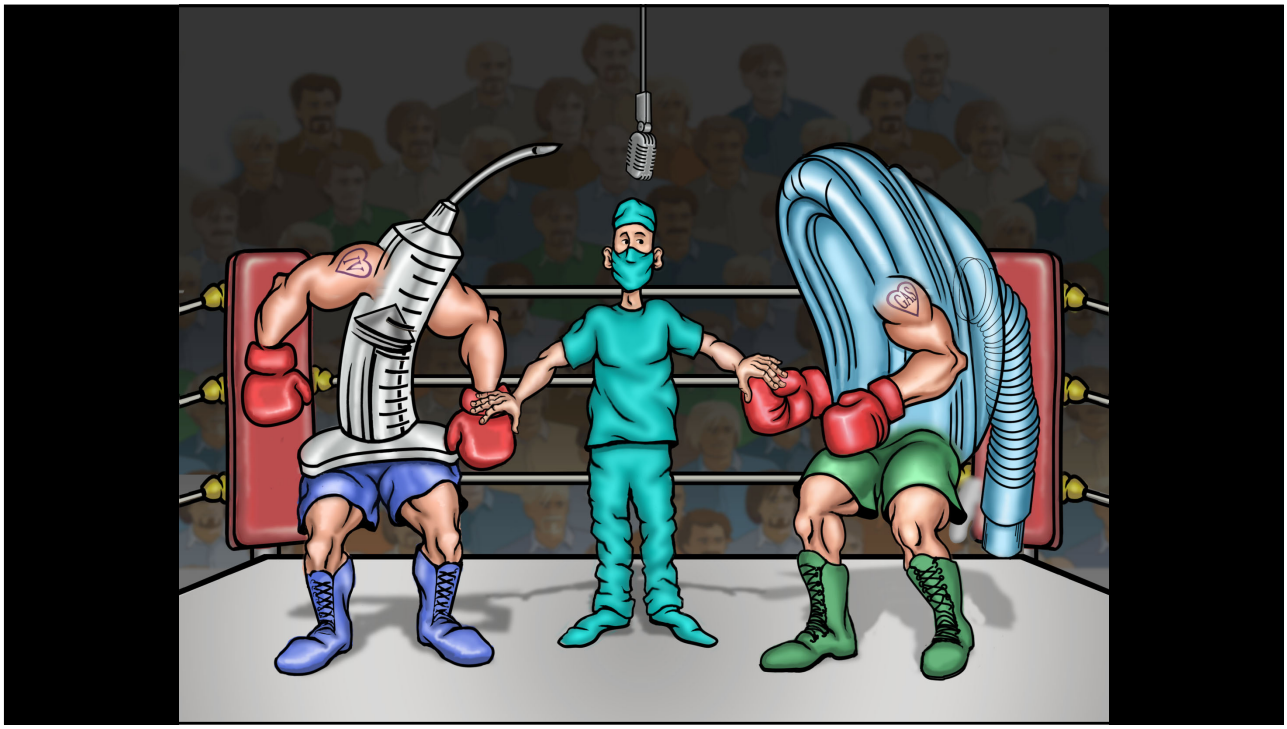

TIVA vs Inhaled Drug Delivery

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.

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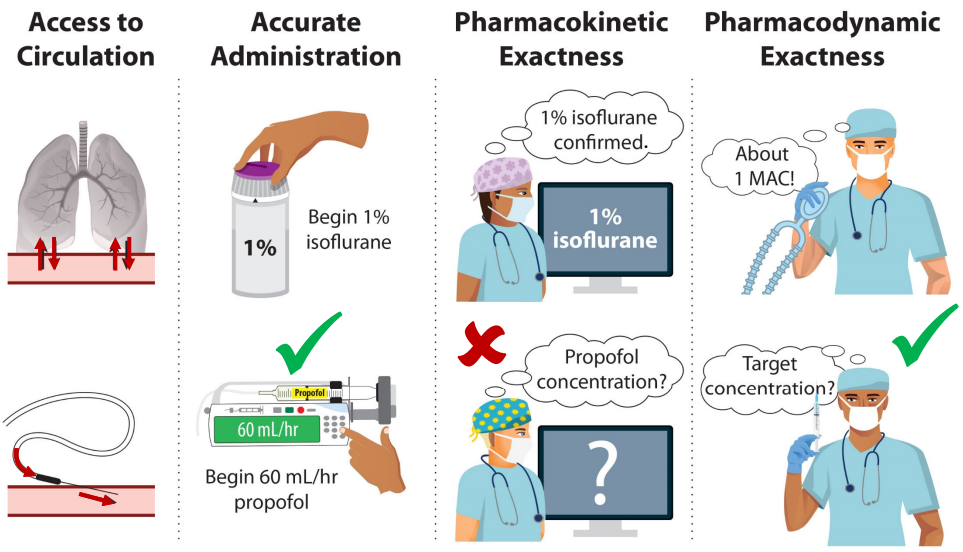
Drug Delivery: TIVA vs. Inhaled (Circa 1990s)



Egan (*J Clin Anesth* 1996)

Anesthesia Posology

Anesthesia posology (the study of drug dosing) is fundamentally different than other specialties of medicine.

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Getting the dose right: anaesthetic drug delivery and the posological sweet spot

K. Kuck* and T. D. Egan

Department of Anesthesiology, University of Utah School of Me

*Corresponding author. E-mail: kai.kuck@hsc.utah.edu

A last try at popularizing the term "posology…."

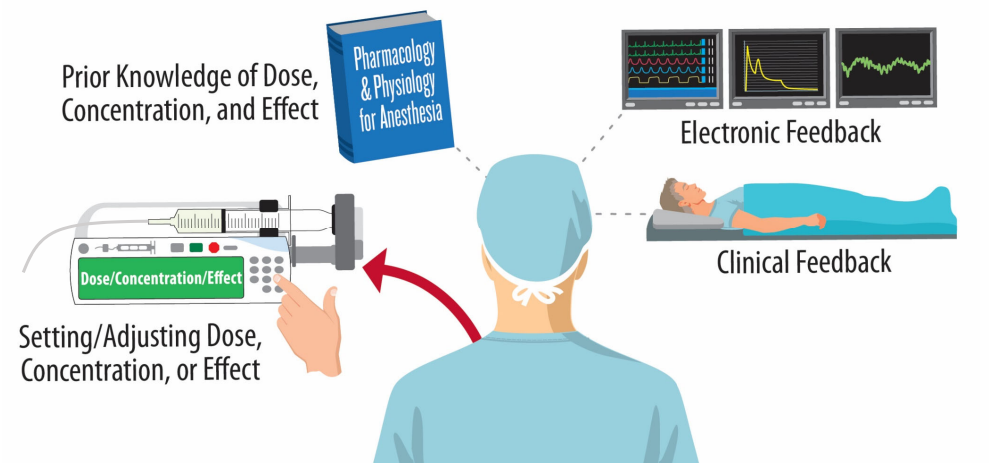
Posology, a scientific term not in common usage, is the science of drug dosage; it is thus a branch of clinical pharmacology (or perhaps a synonym of sorts). Combining the Greek word (how much) and 'logos' (science), posology more simply as 'dosology'. In the posology of a fundamental question anaesthetists must answer ea 'What is the right anaesthetic dosing strategy for patient?'

"Combining the Greek words 'posos' (how much) and 'logos' (science), posology can be thought of more simply as 'dosology'."

In this issue of the *British Journal of Anaesthesia*, van and colleagues[1] report a novel approach to optimizing in anaesthesia. Their study was an attempt to persona get-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[2] and then adjusted them based on the difference between tion and the observation, normalized by their variability. This moves the adjusted system from the *a priori* starting point

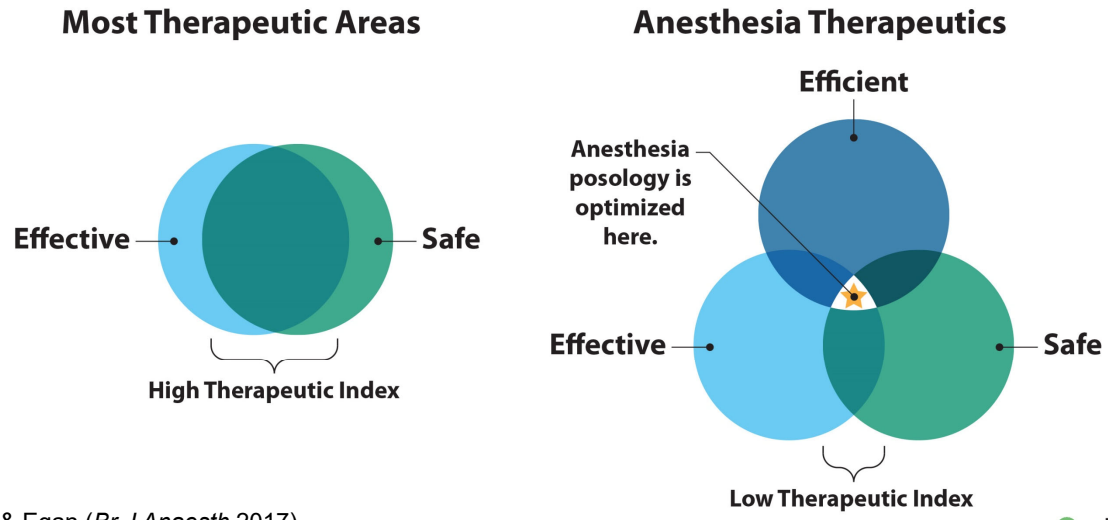
Kuck & Egan (*Br J Anaesth* 2017)

General Approach to Anesthesia Posology



Egan (*Anesth Analg* 2018)

Posology in Anesthesia: A Venn Diagram



Kuck & Egan (*Br J Anaesth* 2017)

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Anesthesia Posology

A surfing analogy is helpful in understanding the modern approach to anesthesia posology.

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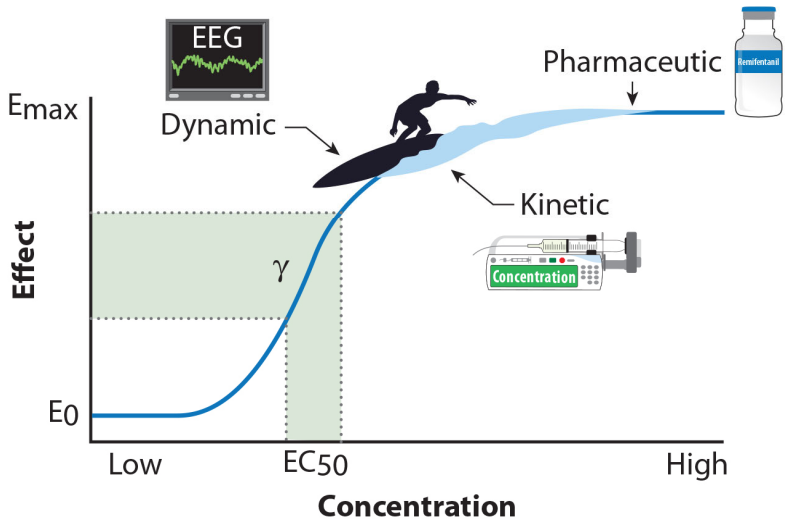
Posology in Anesthesia: A Surfing Analogy



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Egan & Shafer (Anesthesiology 2003)

TIVA Practice Domains

There are three TIVA practice domains (i.e., dose, concentration, & effect). The effect domain is optimal.

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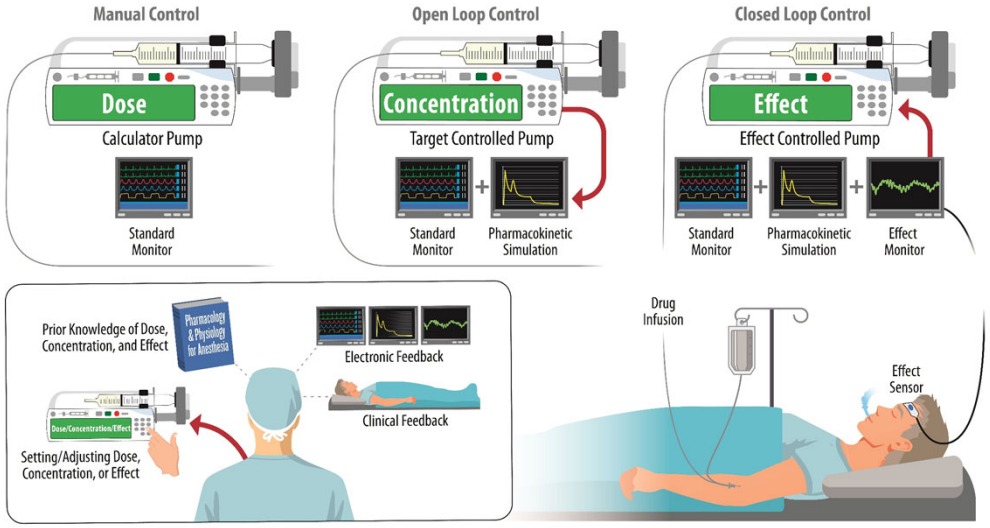
Three TIVA Practice Domains



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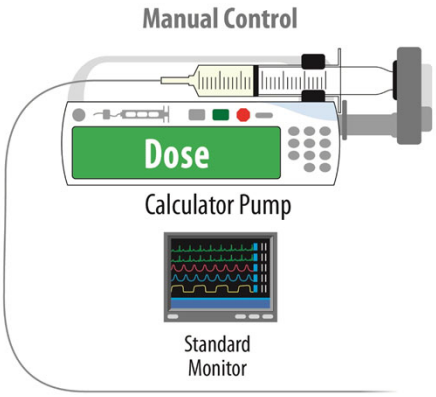
Egan (*Anesth Analg* 2018)

The Dose Domain

- ✓ Simple to use
- ✓ Familiar to all



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

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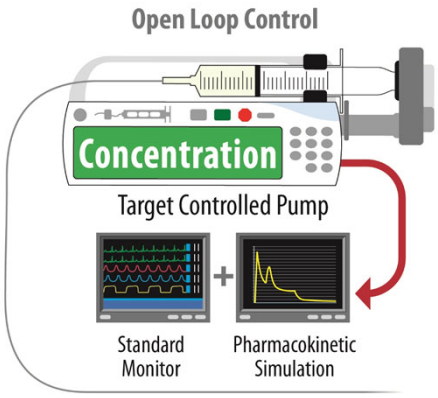
Egan (*Anesth Analg* 2018)

The Concentration Domain

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



- ✓ Ignores intersubject variability
- ✓ Less familiar (USA)

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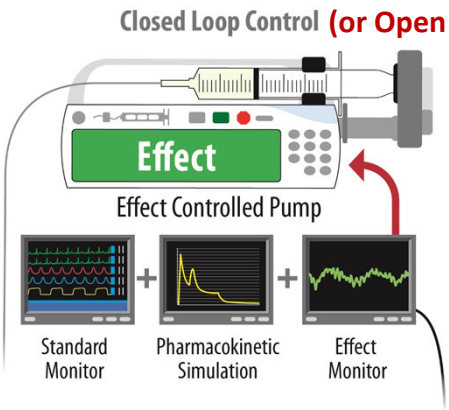
Egan (*Anesth Analg* 2018)

The Effect Domain

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

Most important!



Usually Best!

- ✓ Complicated control system (automated)
- ✓ Suboptimal sensors
- ✓ Less familiar
- ✓ Unintended conse-quences?

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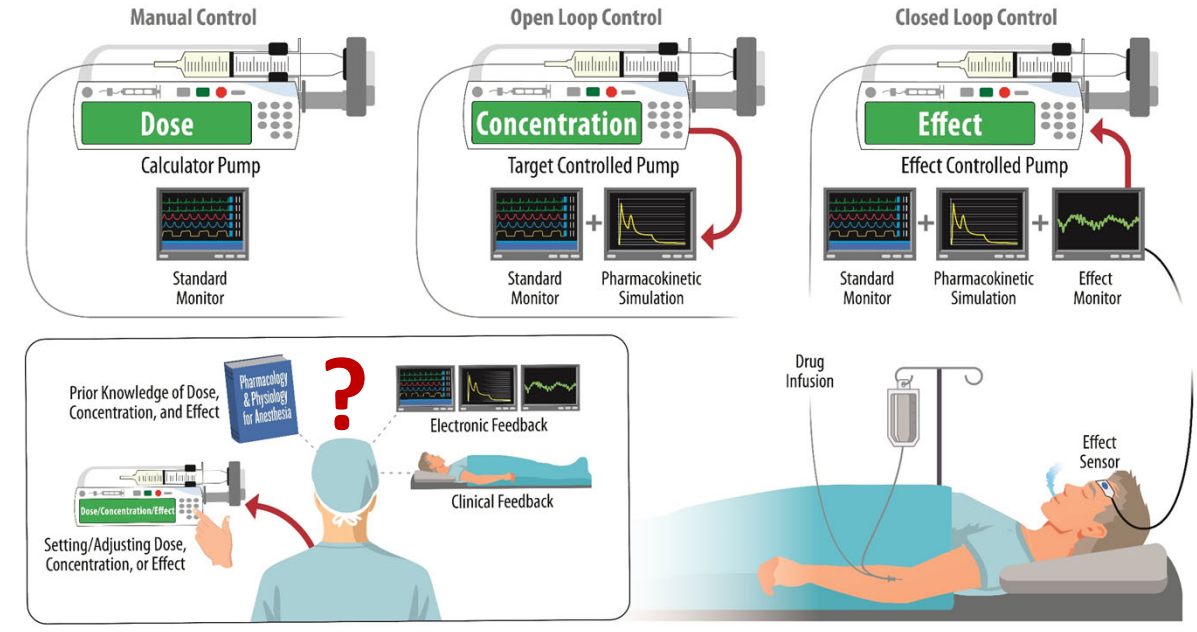
Egan (*Anesth Analg* 2018)



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Egan (*Anesth Analg* 2018)

Crucial Drug Behaviors and TIVA

Certain pharmacokinetic attributes inform TIVA posology for bolus and infusions conditions. These attributes are best understood through PK-PD simulation.

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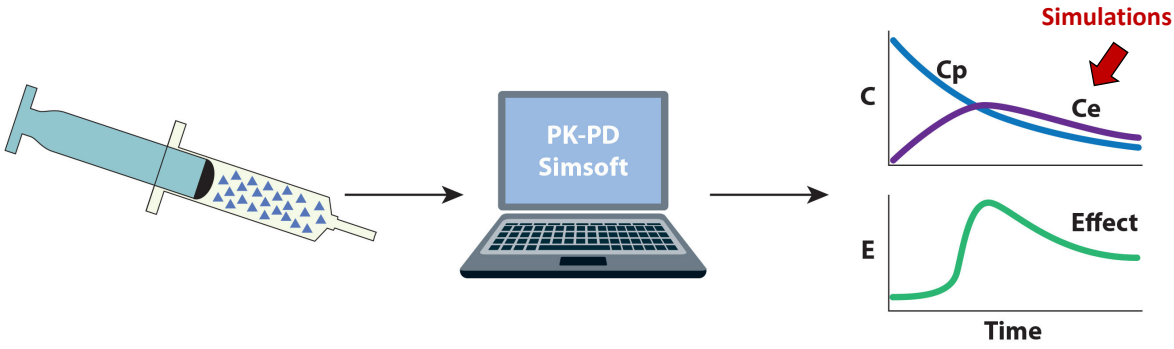
Clinical Inference via PK/PD Simulation



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

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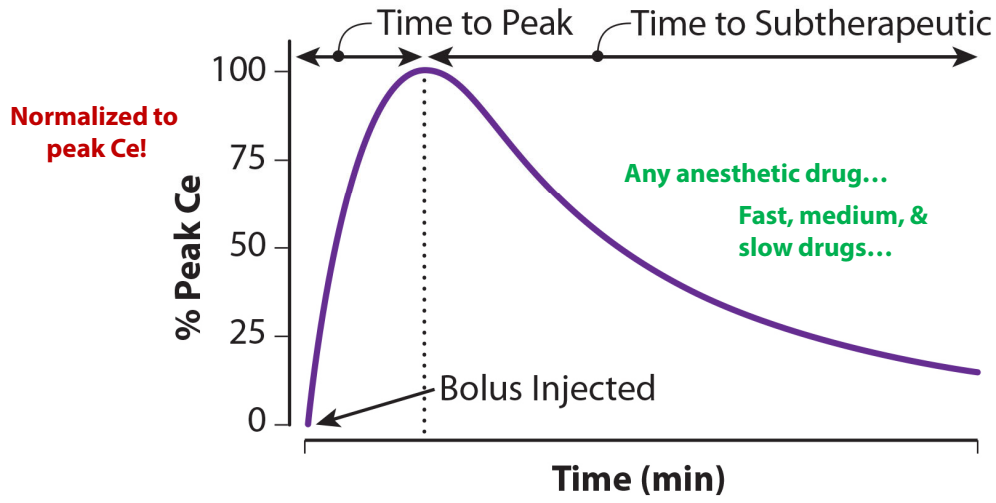
Obara & Egan
(in Hemmings & Egan, Elsevier 2019)

Bolus Front-End & Back-End



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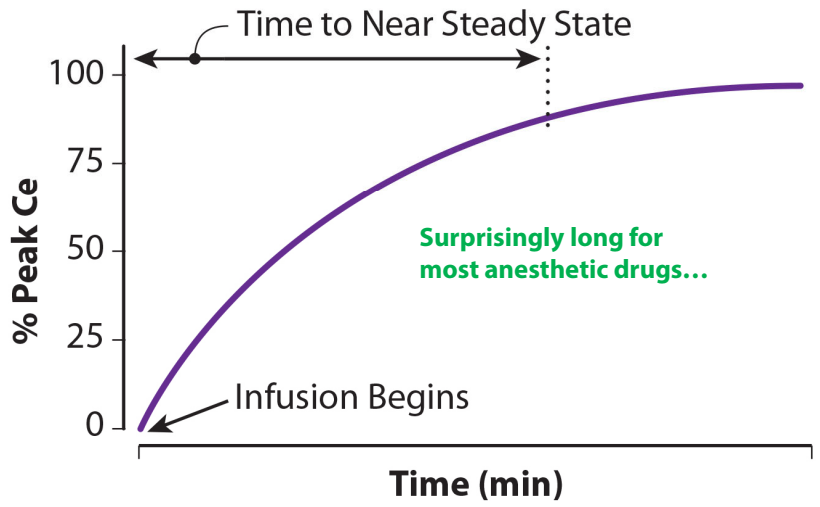
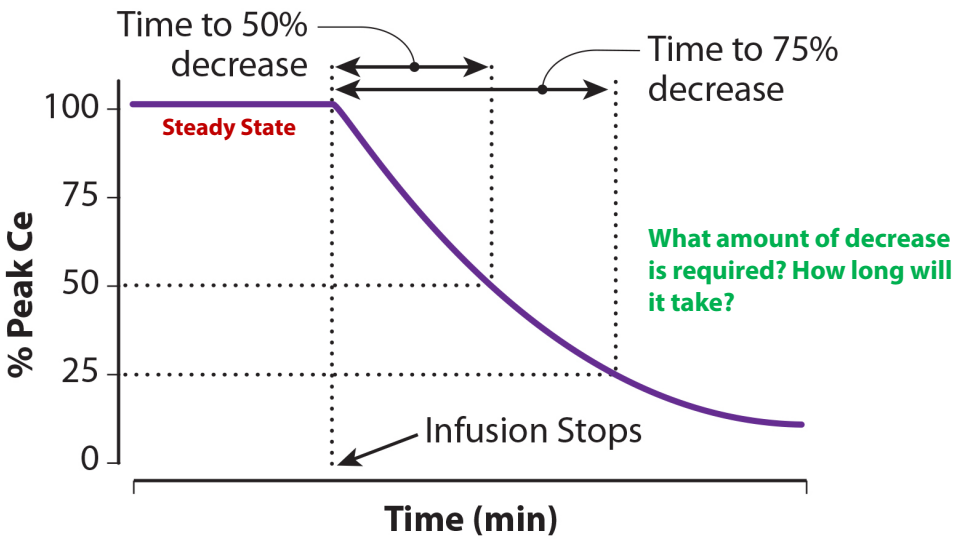
Infusion Front-End



TAKE 5 FOR TIVA

Infusion Back-End



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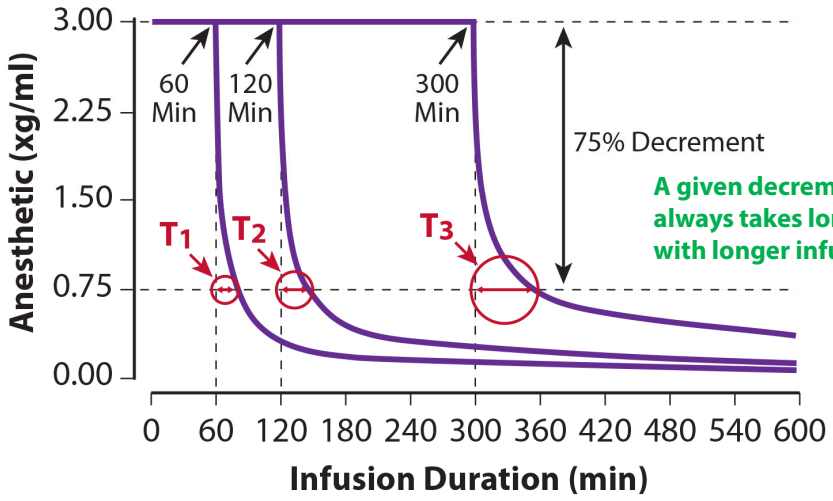
Impact of Infusion Duration



A given decrement almost always takes longer with longer infusions…

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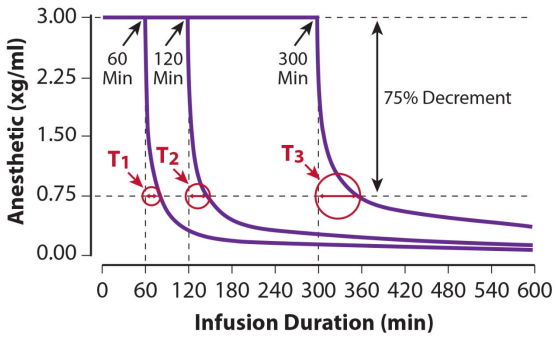
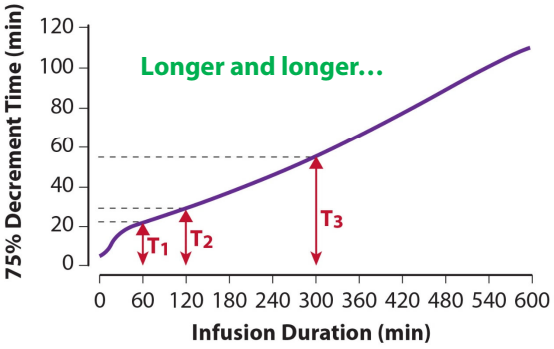
Impact of Infusion Duration



75% Decrement Times



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Crucial Drug Behaviors and TIVA

Certain pharmacodynamic concepts inform TIVA posology. Chief among these are propofol-opioid pharmacodynamic interactions.

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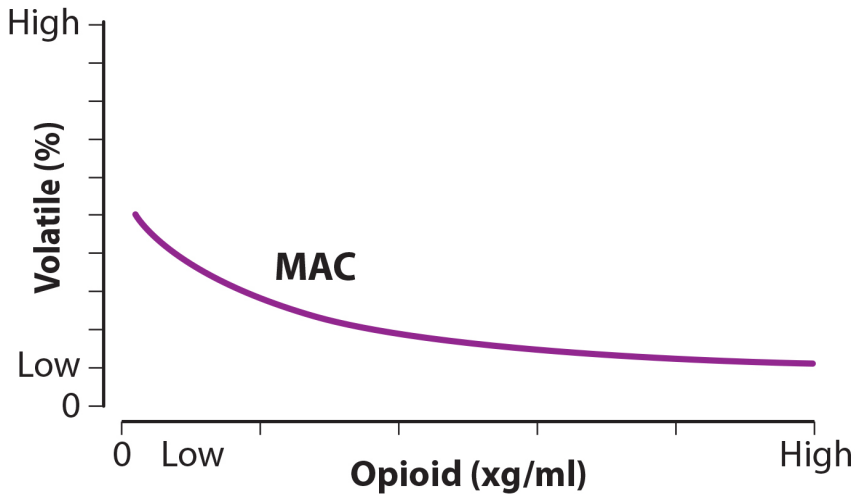
MAC Reduction by Opioids



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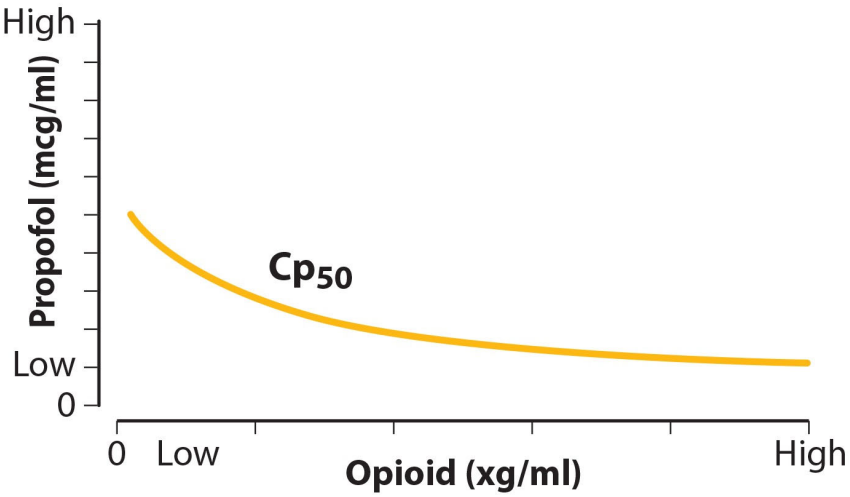
Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol Cp_{50} Reduction by Opioids



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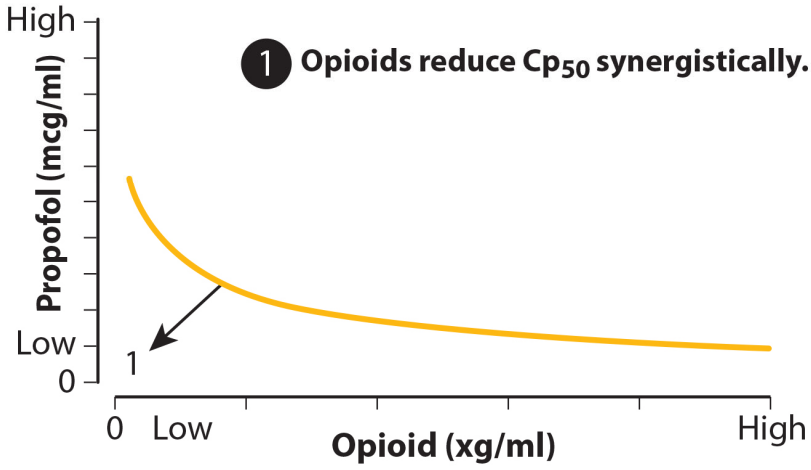
Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol-Opioid PD Interaction



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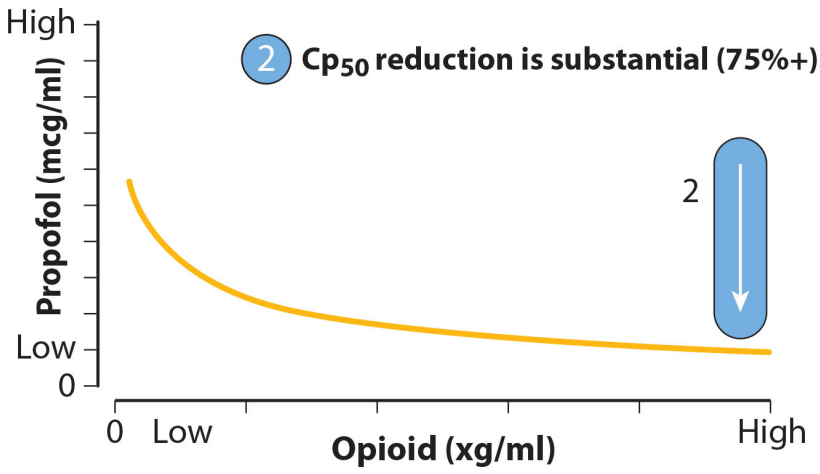

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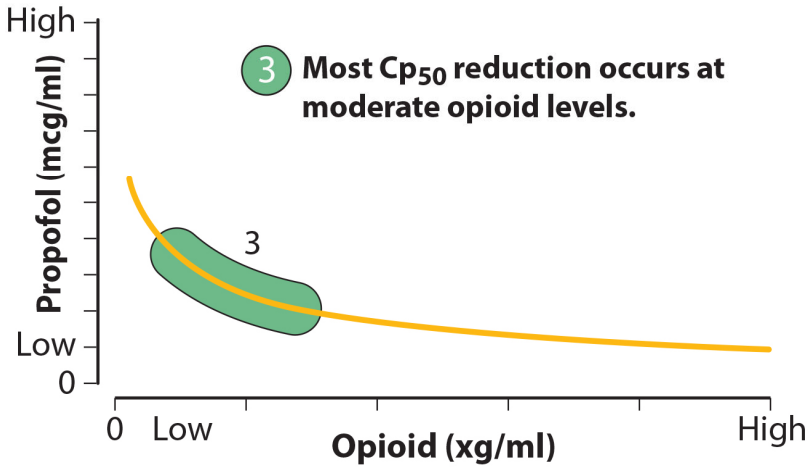

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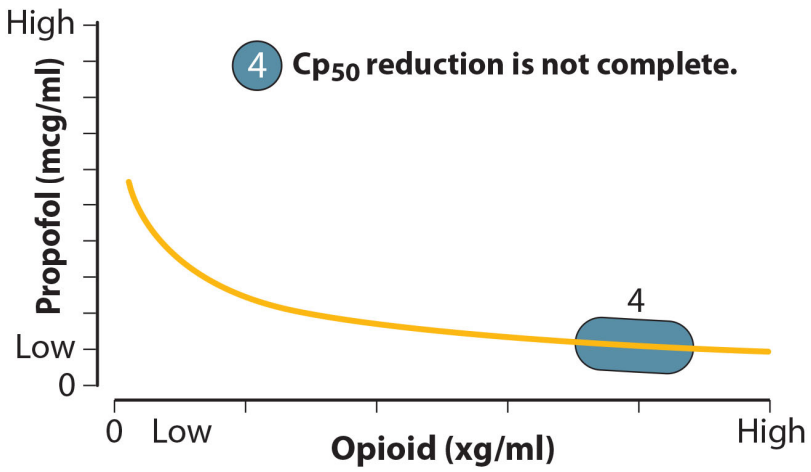

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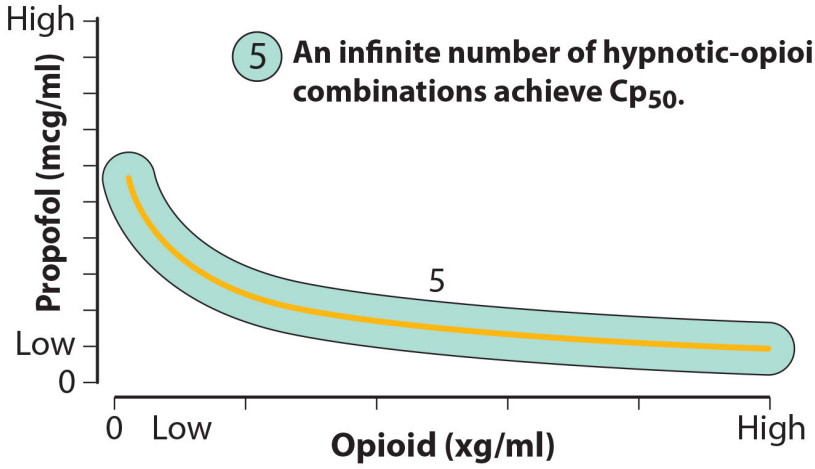

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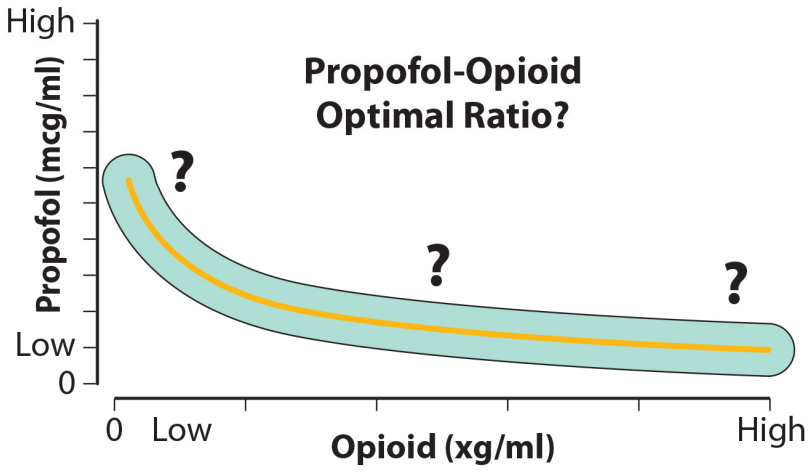
Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol-Opioid PD Interaction



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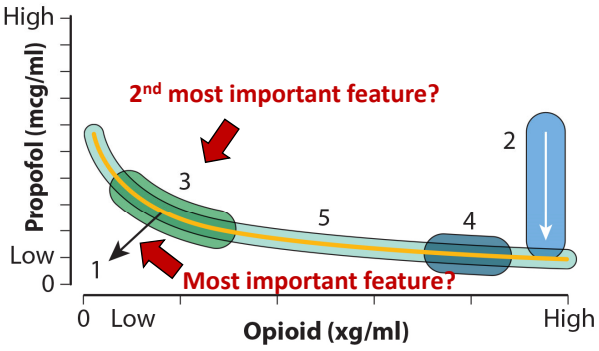
Propofol-Opioid PD Interaction



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}.

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Ogura & Egan (in Hemmings & Egan, Elsevier 2019)

Propofol Clinical Pharmacology & TIVA

Simulation of propofol's pharmacokinetic behavior helps inform posological decisions in TIVA.

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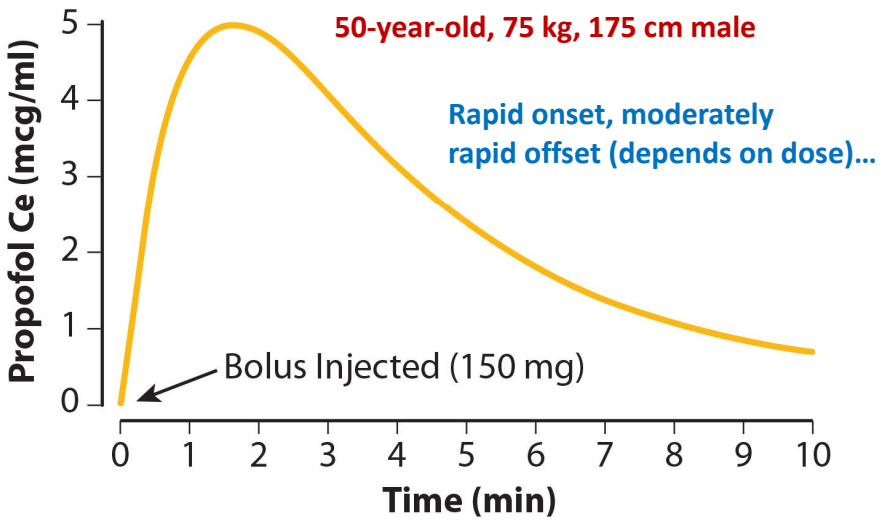
Bolus Front-End & Back-End



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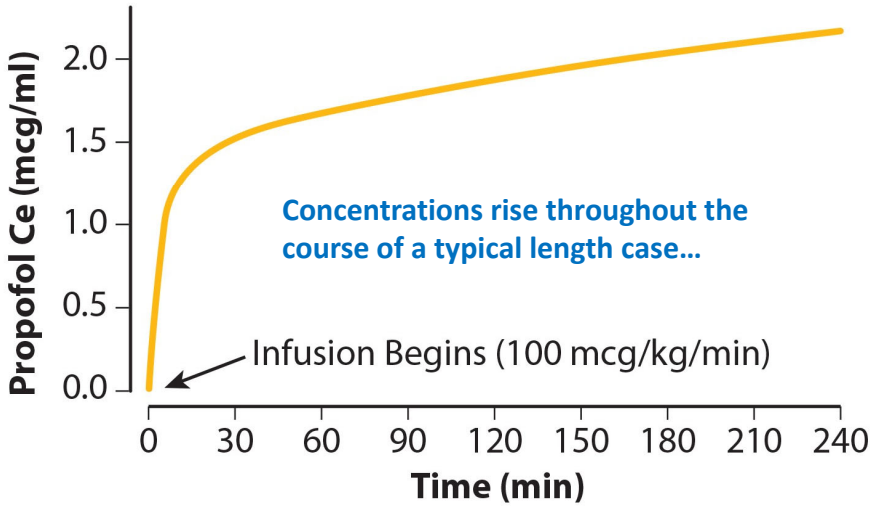
Infusion Front-End



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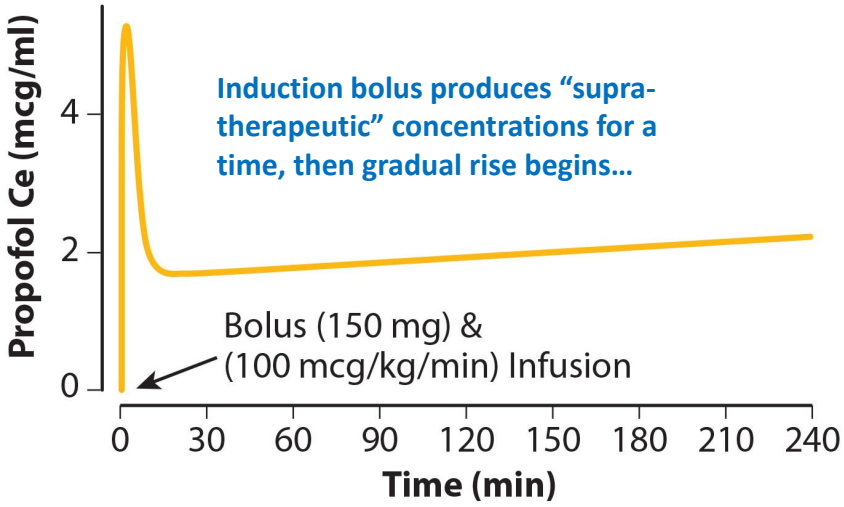
Impact of Loading Dose



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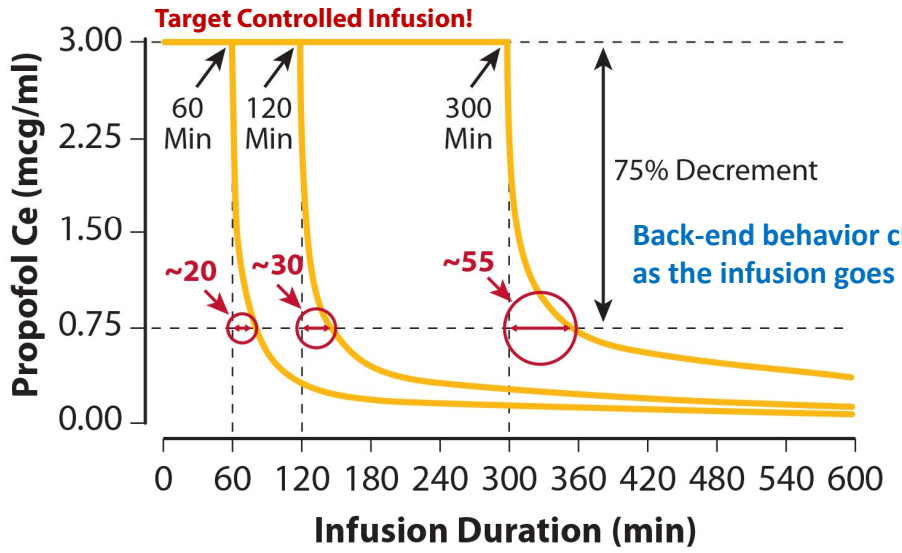
Infusion Back-End



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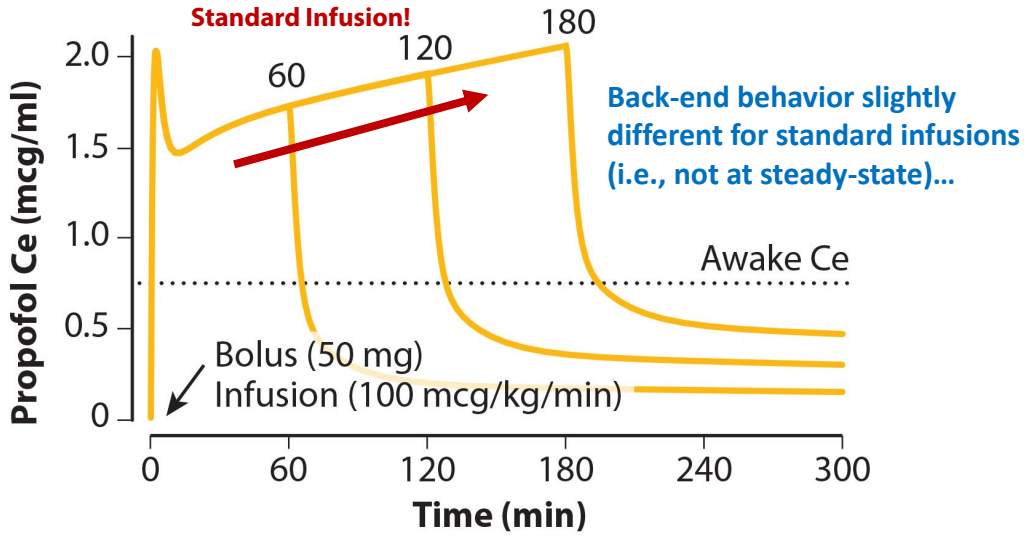
Impact of Infusion Duration



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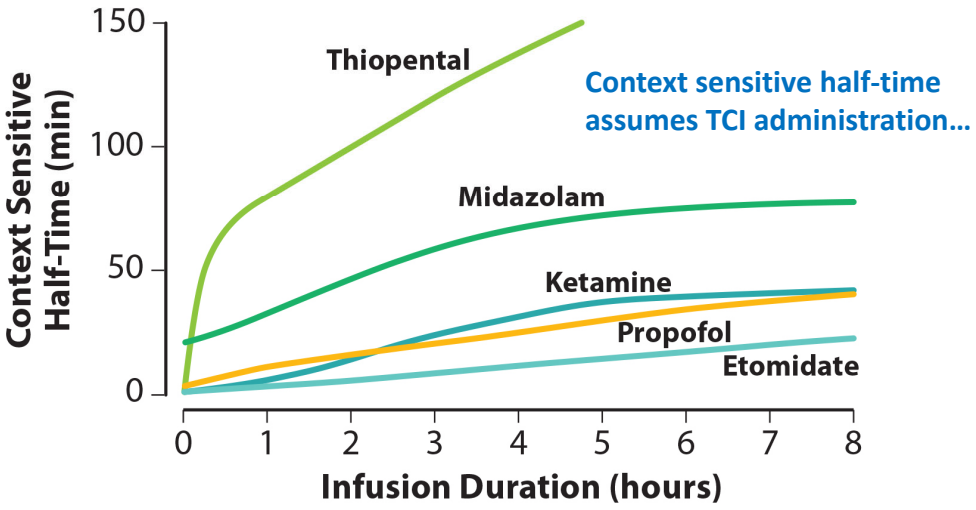
Context Sensitive Half-Time



Context sensitive half-time assumes TCI administration...

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Obara & Egan (in Hemmings & Egan, Elsevier 2019)

Opioid Clinical Pharmacology & TIVA

Simulation of remifentanil and fentanyl pharmacokinetic behavior helps inform posological decisions in TIVA.

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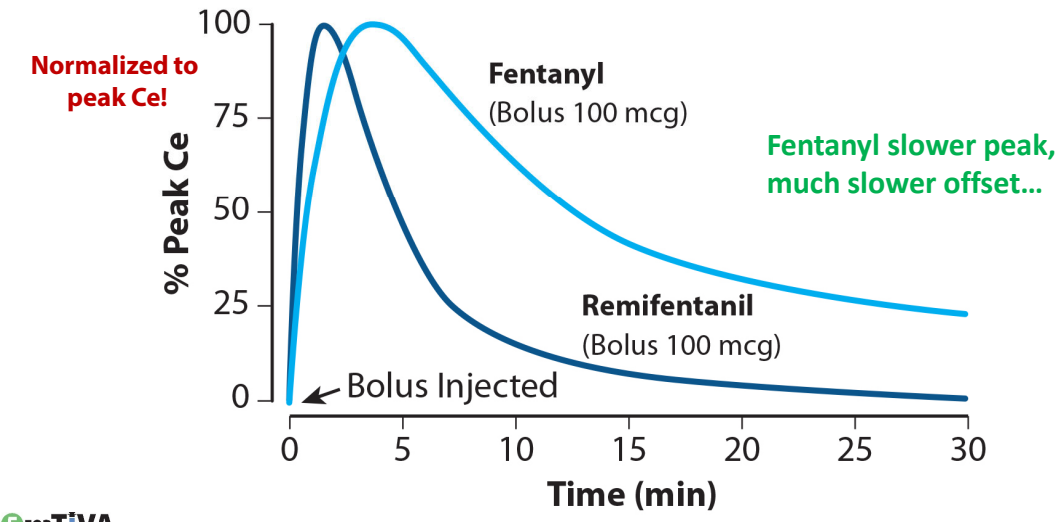
Bolus Front-End & Back-End



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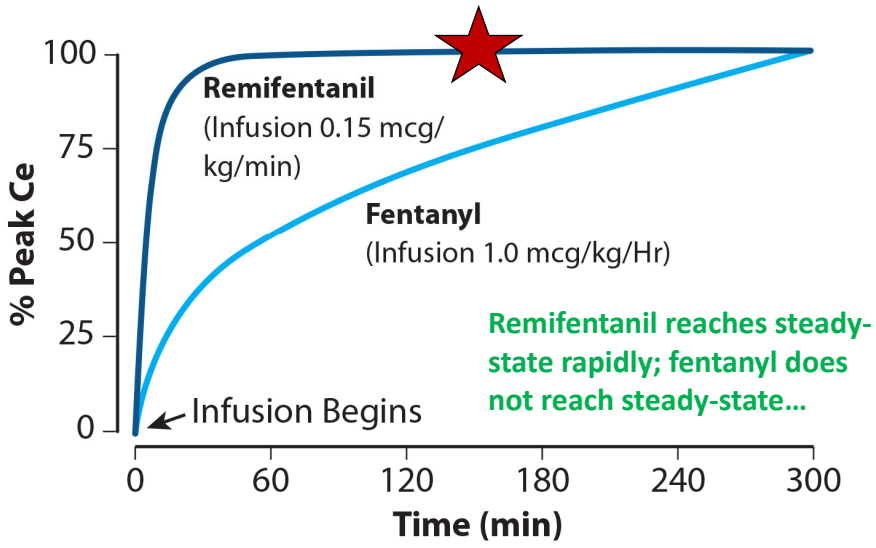
Infusion Front-End



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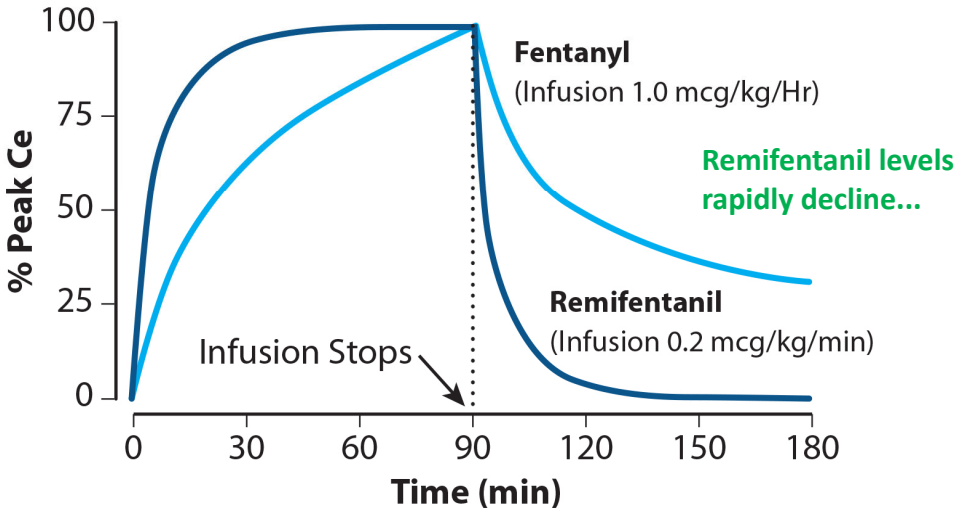
Infusion Back-End



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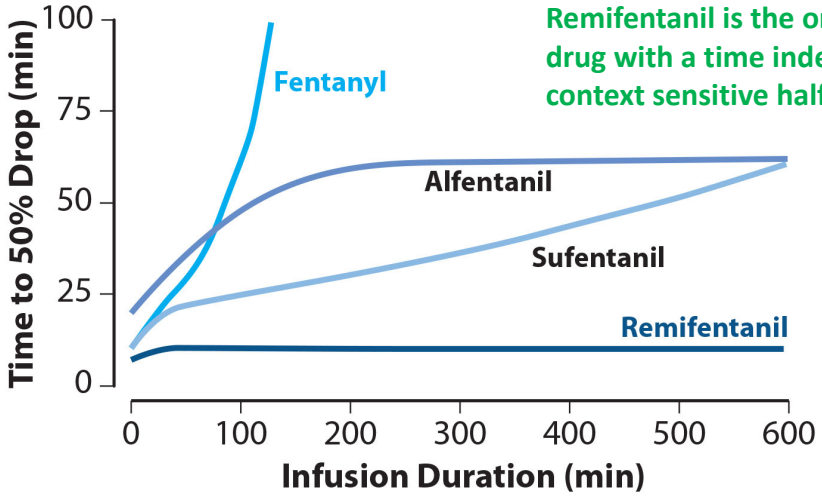
Context Sensitive Half-Time



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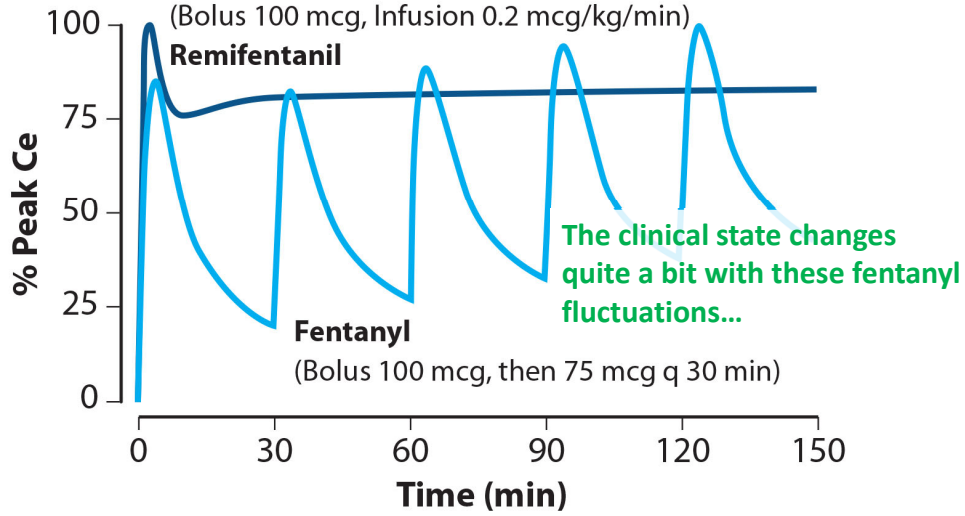
Egan *et al* (*Anesthesiology* 1993)

Impact of Infusion vs. Bolus



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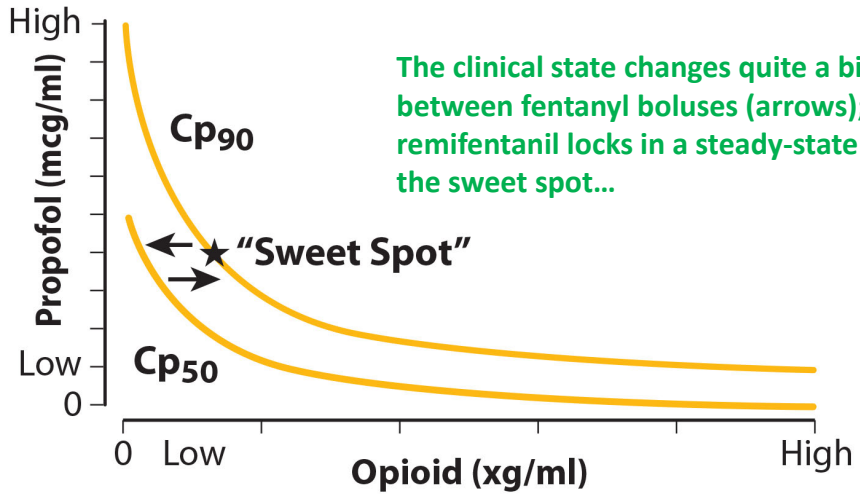
Disruptive Impact of Boluses



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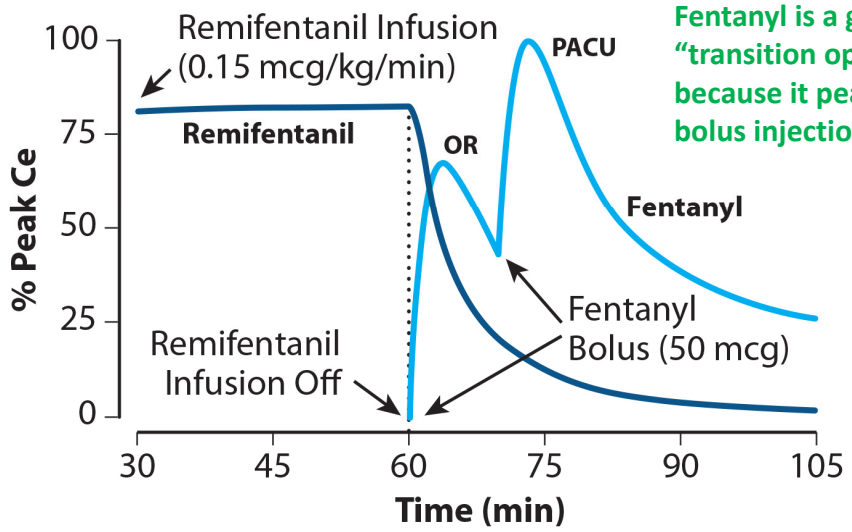
Transition Opioid



Fentanyl is a good "transition opioid" because it peaks after bolus injection quickly...

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Tips and Tricks of the TIVA Trade

Certain practical tips are helpful for successful TIVA practice.

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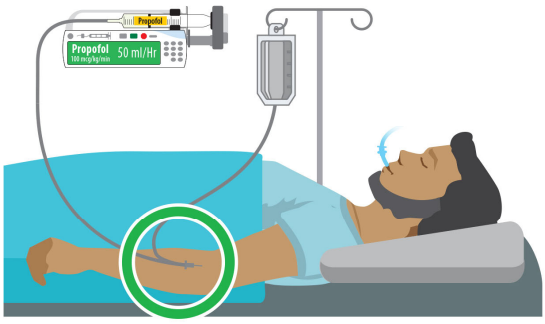
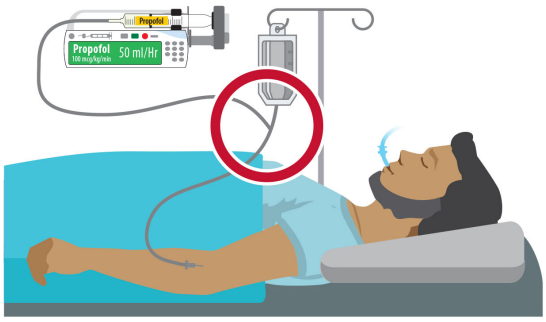
Infuse Close and Secure



Infuse Close to IV



Do Not Infuse Far from IV

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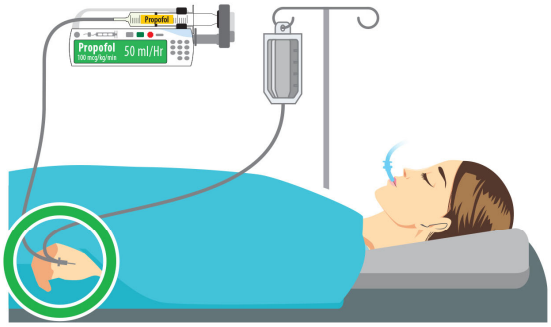
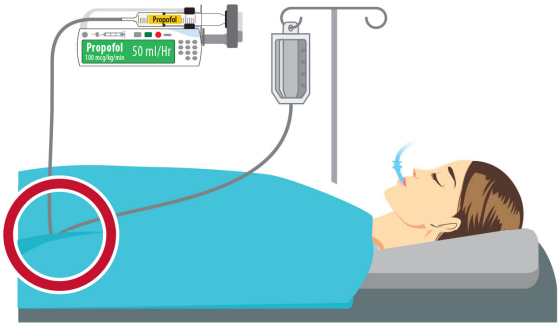
Keep IV Visible



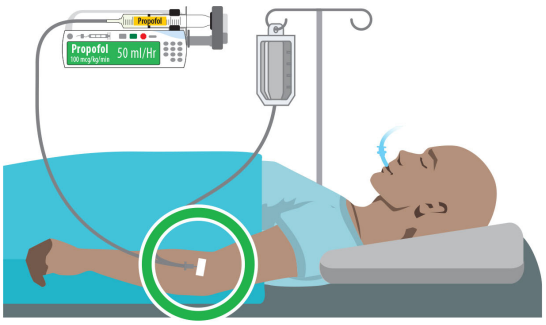
IV Visible: Optimal



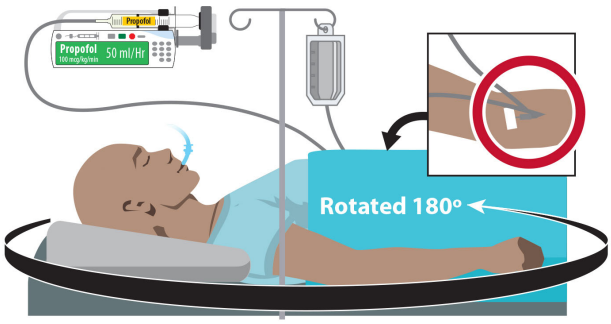
IV Not Visible: Suboptimal

TAKE 5 FOR TIVA

Be Alert for Infusion Disruption



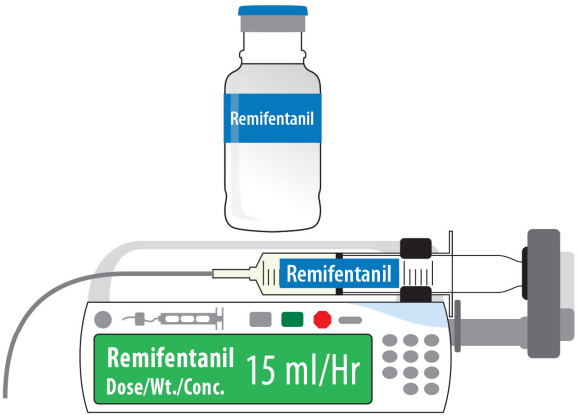
IV Flowing



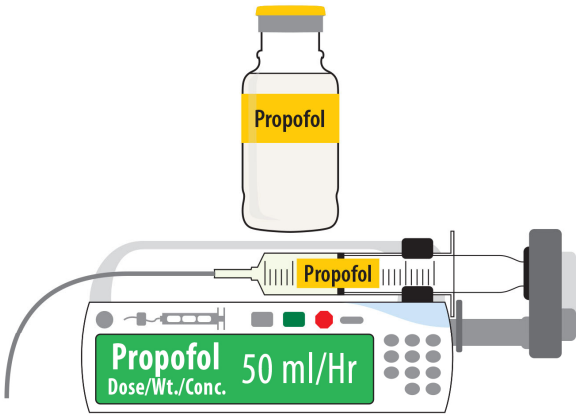
IV Kinked, **Not** Flowing

TAKE 5 FOR TIVA

Check for Pump Programming Error

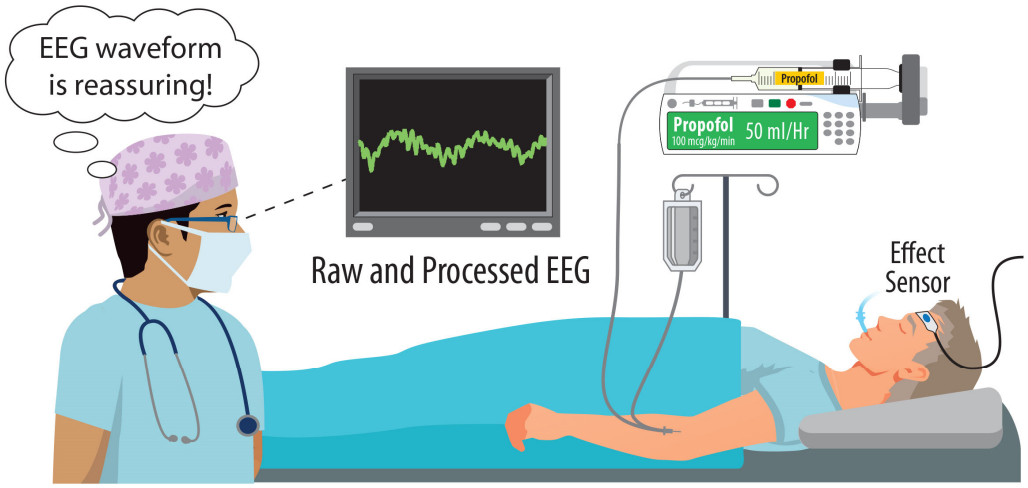


Typical Rate = 10-20 ml/Hr



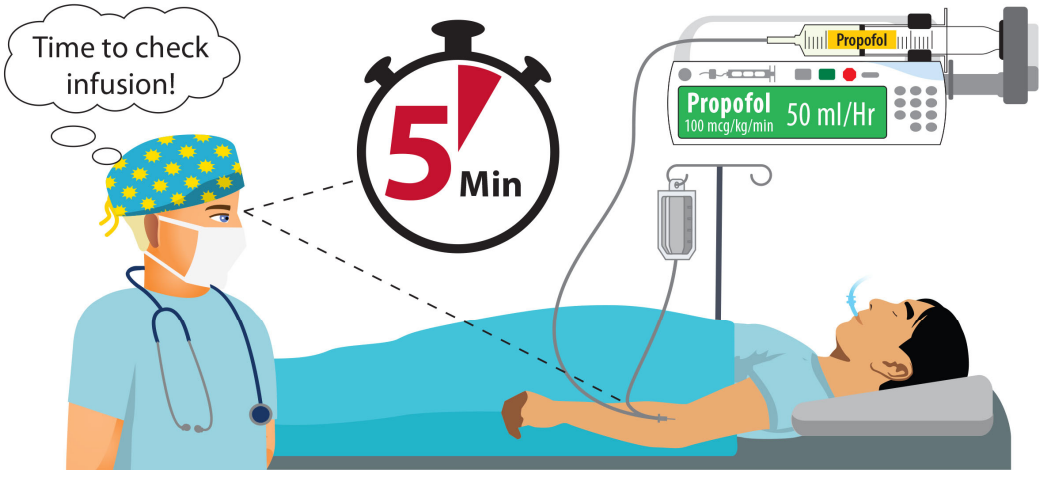
Typical Rate = 40-60 ml/Hr

Consider Using EEG



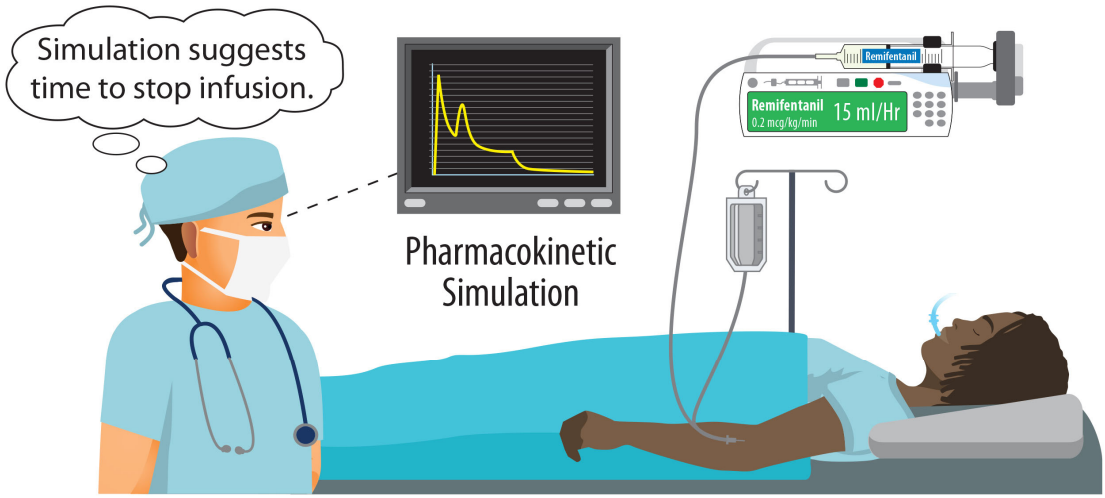
TAKE 5 FOR TIVA

Check Infusions Frequently



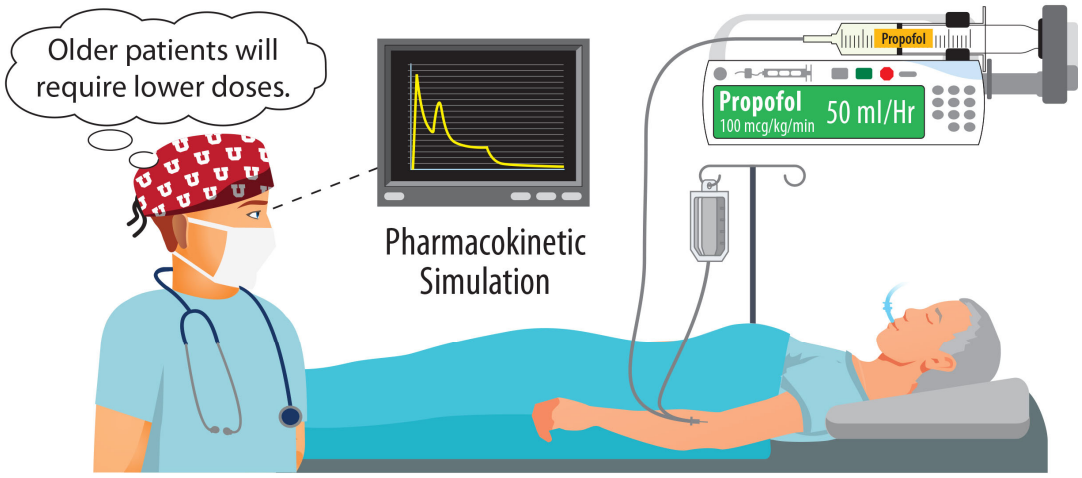
TAKE 5 FOR TIVA

Consider Real Time PK/PD Simulation



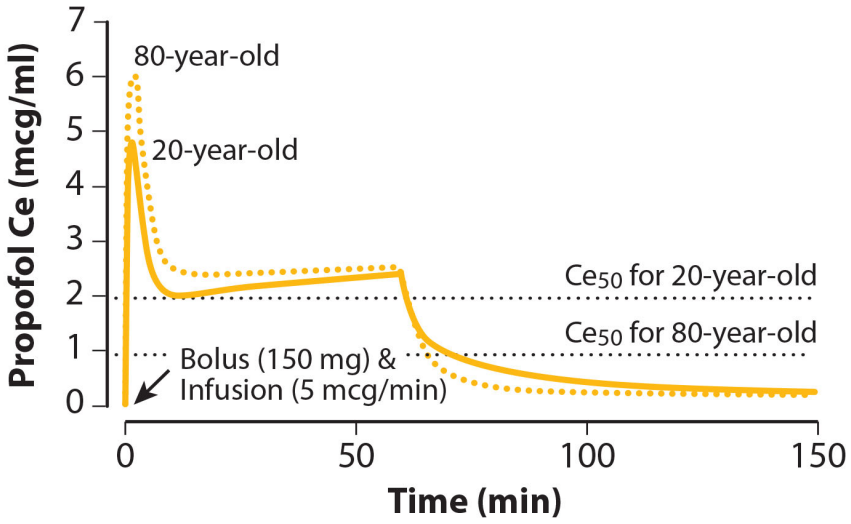
TAKE 5 FOR TIVA

Adjust Dose for Senior Patients



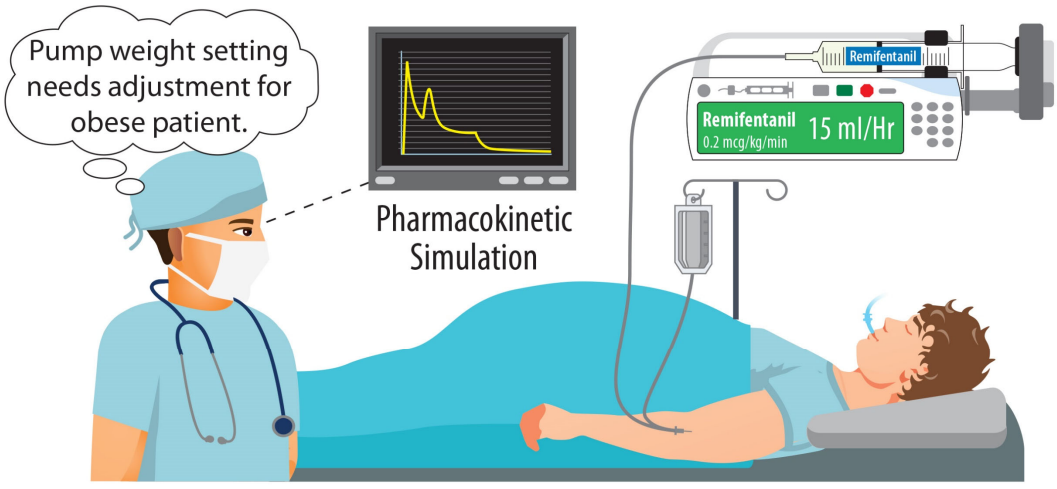
TAKE 5 FOR TIVA

Impact of Age



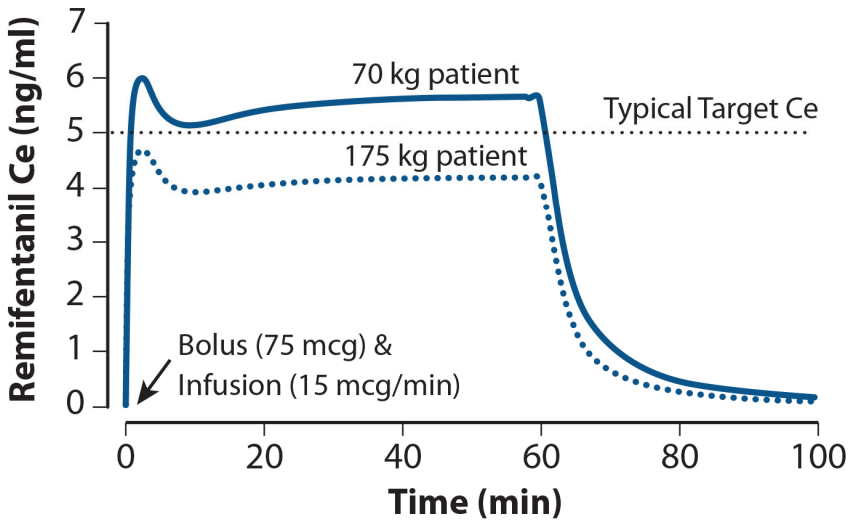
Obara & Egan (in Hemmings & Egan, Elsevier 2019)

Adjust Pump Weight Setting for Obese Patients



TAKE 5 FOR TIVA

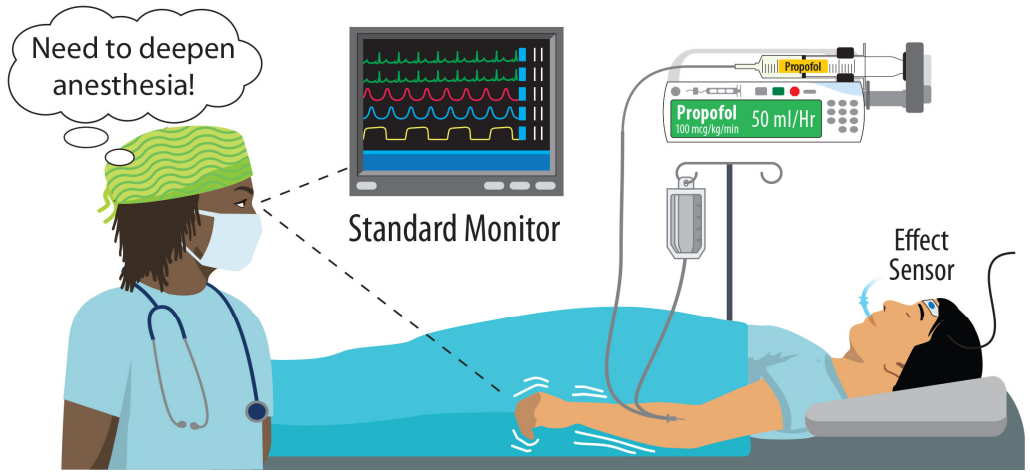
Impact of Body Weight



TAKE 5 FOR TIVA

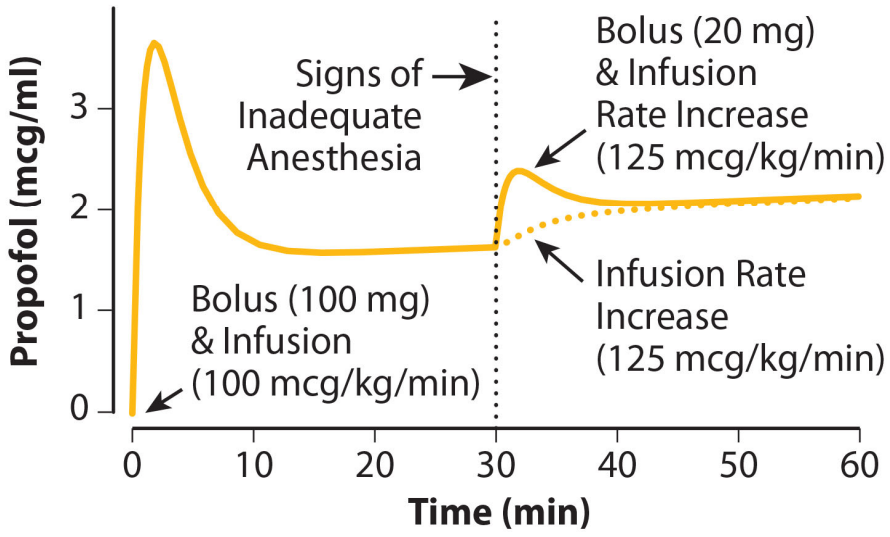
Obara & Egan (in Hemmings & Egan, Elsevier 2019)

Deepen Anesthesia with Small Bolus and Infusion Rate Increase

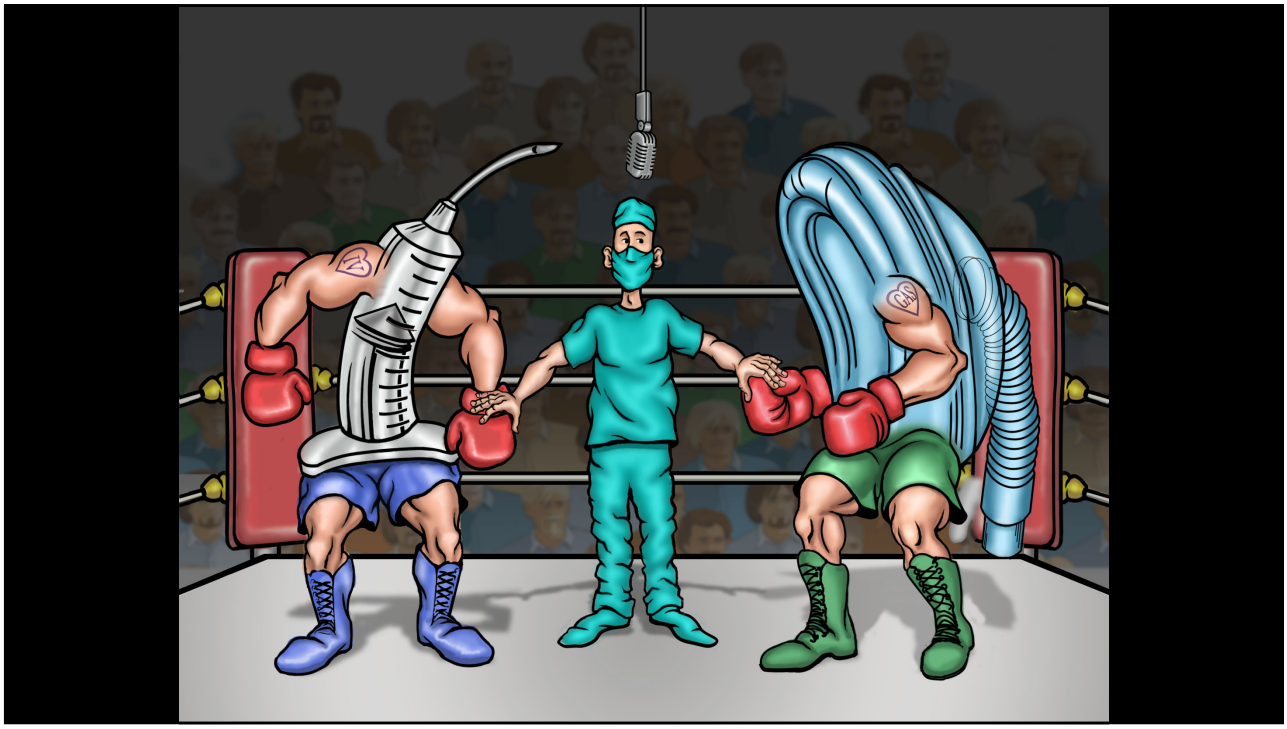


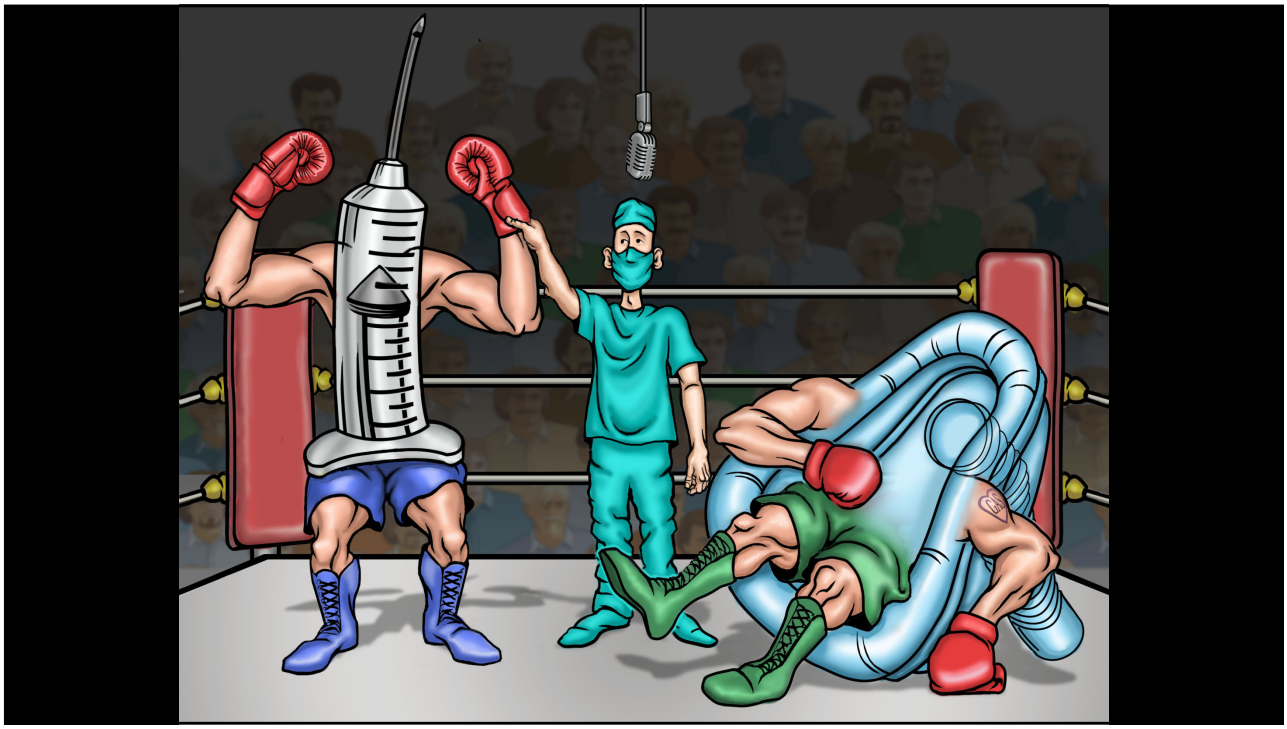
TAKE 5 FOR TIVA

Impact of Bolus & Infusion



TAKE 5 FOR TIVA



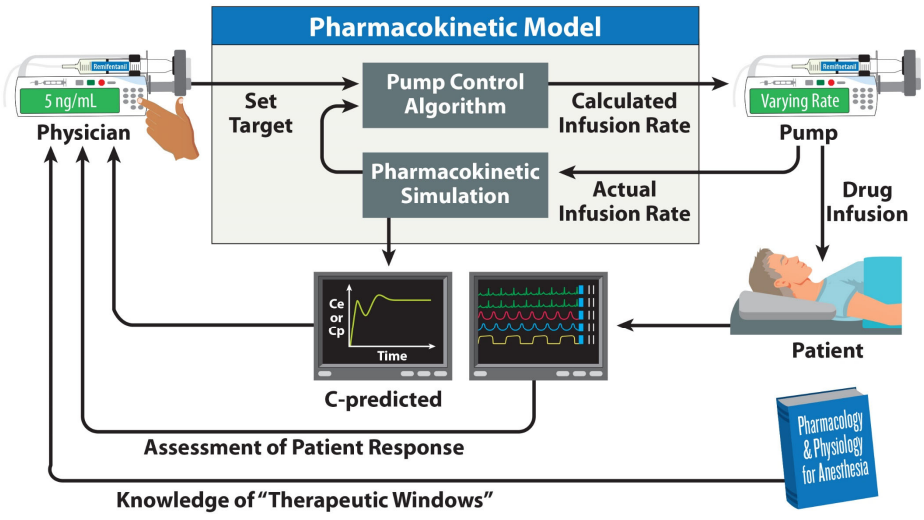


MPOG
MULTICENTER PERIOPERATIVE OUTCOMES GROUP

THRIVE

Supplementary Material

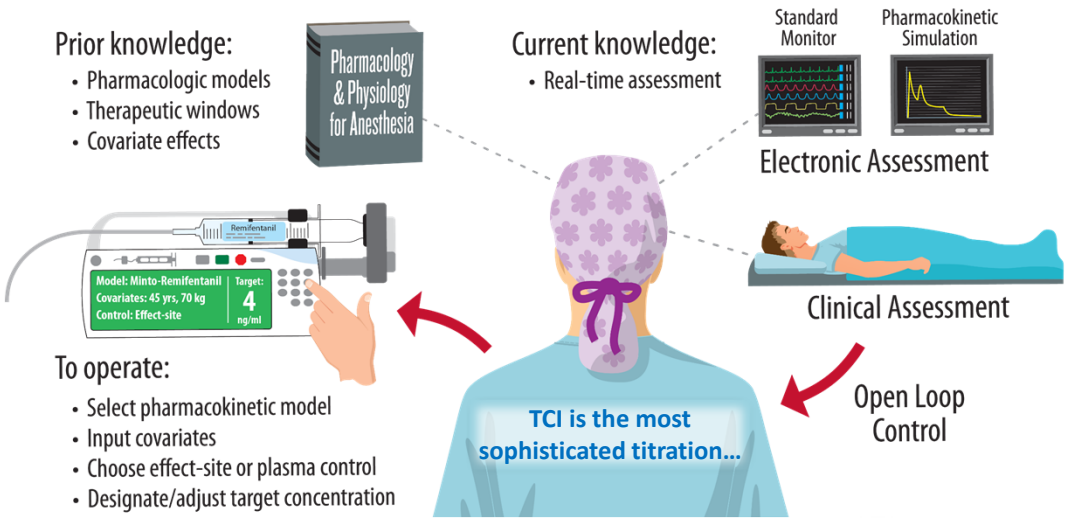
Target Controlled Infusion System



TAKE 5 FOR TIVA

Egan (*Anesthesiology* 2003)

Target Controlled Infusion Practice



TAKE 5 FOR TIVA

Egan *et al* (*Br J Anaesth* 2020)