Total Intravenous Anesthesia

A RATIONAL APPROACH TO ANESTHETIC MANAGEMENT

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Wake Forest School of Medicine

Objectives
- Review drugs and methods in TIVA
- Discuss how propofol aids administration of TIVA
- Describe different equipment that makes administration of TIVA safe and effective
- List new drugs and drug combinations that are used to improve TIVA
- Outline medical conditions, disease processes and types of surgery that lend themselves to TIVA for GA
- Discuss contraindications to TIVA for GA

Drug administration

"Intravenous agents administered by manual bolus on a dose/kg basis is probably as old-fashioned as administration of volatile agents by the Schimmelbusch mask."

Armin Holas MD, University of Graz, Austria.

Why Intravenous anesthetics?

Safety
- Hemodynamic control
- Rapid titration
- Avoid vasodilatation, expansion of gas cavities
- Reduced PONV
- Occupational exposure
- Smooth emergence, less hangover
- Avoid MH risk
- Cost benefit

Why Intravenous Anesthetics?

- Improved mucociliary transport
- Reduced PONV
- Less effect on hepatic enzymes
Advantages of TIVA

- Improved V/Q matching
- Reduced stress response.
- Improved surgical field (bleeding)

Advantages of TIVA over balanced

- Improved CPP, less interference with SSEP, MEP, AEP; Minimal post-op side-effects; potential neuroprotective effects via antioxidant properties.
- Better preservation of cerebral autoregulation vs. volatile
  - Ishikawa, Masui. 2003;52(4):370-7
  - McCulloch Anesthesiology. 2007;106(1):56-64.

Advantages of TIVA over regional

- Following TKA, better pain scores, less N & V, shorter length of stay, compared to bupivacaine spinal.

Not a panacea

- Pre-conditioning/tissue protection from volatiles is a nice side-effect.
- Remi-Des allowed adequate SSEP, with faster emergence then Remi-prop

Not a panacea

- + Titratable, but no diff in shivering, PONV, HTN.
  - Wong Af. Eur Anaes 2006;23(7):586-90
- No diff in pain; more shivering with TIVA.
- Cost. (But less PONV)
  - Rohm KD. Acta Anaesthesiologica Scandinavica. 2006;50(1):14-8

Propofol: Anesthesia’s wonder drug
Recovery profile of propofol
Stages of recovery after anesthesia

- Early (emergence)- Rapid and predictable
- Intermediate- Early return of cognitive and psychomotor function. Early time to discharge (?)
- Low incidence of PONV

Reduced risk of postoperative vomiting
Meta-analysis of studies: propofol vs volatiles

<table>
<thead>
<tr>
<th>Inhalational agents</th>
<th>Isoflurane (maintenance)</th>
<th>Desflurane or sevoflurane (maintenance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in risk of vomiting after 'Diprivan' (induction and maintenance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 studies</td>
<td>42 studies</td>
<td>6 studies</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
<td>p &lt; 0.0001</td>
<td>p = 0.003</td>
</tr>
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</table>


Why infusions?
Avoid over and undershoot of dosage
Avoid latency in reaching effect site
Reduce workload intraoperatively
More rapid awakening
Continuous infusions reduce total drug usage by 25-50%
Less respiratory depression
Discharge times reduced 30%¹

¹White FE. Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology. 1983;59(4):294-300.
Why infusions?
Reduce workload intraoperatively
Reduce total drug usage by 25-50%

Why infusions?
More rapid awakening
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Discharge times reduced 30%

Why infusions?
Patients met PACU discharge criteria 30 minutes faster with TIVA

Reliability of discharge improvement


Reliability of discharge improvement

Good open drop ether mask Strength of pulse
Better concentration-controlled vaporizers Deliver MAC level
Best RGM, neuro monitors Titrates to effect-site concentration and response

A comparison of the recovery times of desflurane and isoflurane in outpatient anesthesia
LISA BRAGA-MONTES, CRNA, MSN
MICHAEL P. RIEKER, CRNA, MS
Winston Salem, North Carolina

...The second confounding issue to address was the definition of recovery. We identified various time intervals that may influence a patient’s discharge time. These factors include a minimum length of stay policy, a requirement to take oral fluids, or simply the unavailability of a physician to write discharge orders. One study found that in 10% of patients, discharge was delayed at least 30 minutes after discharge criteria were met.
Why now?

Historical perspective
Intravenous anesthesia

<table>
<thead>
<tr>
<th>Good</th>
<th>IV bolus</th>
<th>Estimate time for recovery, based on $\beta_{1/2}$</th>
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<tr>
<td>Better</td>
<td>Infusion pump</td>
<td>Titrate according to context-specific half-time</td>
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<tr>
<td>Best</td>
<td>Rapid recovery drugs, target-controlled infusion pumps</td>
<td>Titrate to effect-site concentration and response</td>
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TIVA equipment

“Total intravenous anesthesia will supercede inhalational anesthesia in pediatric anesthetic practice”


Specific indications for TIVA

- Need for precision control
- Airway procedures
- Remote locations
- MH susceptible
- Neurosurgery
- Neuro monitoring
- Neuromuscular disorders
- PONV risk
Effect on PONV

- PONV similar between Propofol TIVA and Sevo + Dolasetron in high-risk patients. Late PONV was worse in TIVA group.
  - White, British Journal of Anaesthesia. 98(4):470-6, 2007

- PONV similar between TIVA without anti-emetic and volatile + anti-emetic
  - Paech Anaesth Intensive Care 10:123-9

- TIVA (without N₂O) equally effective as any anti-emetic as independent factor reducing PONV

Disadvantages

- Acquisition costs
- Controlled substance accounting
- Set-up and use greater workload than vaporizers
- Early or late respiratory depression
- Opioid side-effects- biliary, muscle rigidity, GI motility, pruritus
- Adverse events if IV line disrupted

Infusion administration

| Good | IV bolus | Estimate time for recovery, based on β₁/₂
<table>
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Forget about elimination half-life

- A useless measure to guide anesthetic administration
- As many half-lives as distribution compartments
- Takes no account of time course at effect site
  - Pentothal- half-life = hours
    - duration = depends on administration i.e., depends on CONTEXT

Pharmacokinetic Models

- Single compartment distribution
  - Half-life
- Two-compartment distribution
- Multicompartmental distribution
Multicompartmental concept

Distribution of people at a party

Foyer

% of guests

Time (hours)

0 1 2 3 4

Open three-compartment PK model

Context-sensitive half-time

Context-sensitive alterations in propofol kinetics

Context-sensitive half life vs. necessary decrease


**Key effect site concentration levels**

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Alfentanil</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction and Intubation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ IV induction agent</td>
<td>3-5 ng/ml</td>
<td>250-400</td>
<td>0.4-0.6</td>
</tr>
<tr>
<td>O₂/N₂O only</td>
<td>8-10</td>
<td>400-750</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N₂O/Vapor</td>
<td>1.5-4</td>
<td>100-300</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>O₂/N₂O only</td>
<td>1.5-10</td>
<td>100-750</td>
<td>0.25-1.0</td>
</tr>
<tr>
<td>O₂ only</td>
<td>15-60</td>
<td>1000-4000</td>
<td>2-8</td>
</tr>
<tr>
<td>Adequate Ventilation</td>
<td>2</td>
<td>125</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Context-sensitive half life vs. necessary decrease**

<table>
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<tr>
<th>Maintenance</th>
<th>Sufentanil ng/ml</th>
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</tr>
<tr>
<td>O₂ only</td>
<td>2-8</td>
</tr>
<tr>
<td>Ventilation</td>
<td>0.25</td>
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**But that’s the old-fashioned way...**

Target-controlled infusions eliminate all that thinking...

Computer-driven infusion pumps are programmed with pharmacokinetic data for specific drugs in a range of patient types. The anesthetist sets the desired blood level and the pump does the rest.

**TCI equipment**

**Measured versus calculated blood propofol concentrations during ‘Diprifusor’ TCI administration of propofol in 46 patients.**

**Loading dose schemes by Diprifusor (propofol TCI program)**

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“Cardiac” induction by Diprifusor


TCI safety mechanisms
- Validated pharmacokinetics
- Compensation for interrupted infusion
- Automatic shutdown in case of malfunction
- Electronic tags on pre-filled syringes (diprivan) to prevent wrong-drug in pump

Tagged, prefilled syringes for use with ‘Diprifusor’ target-controlled infusion systems

TCI Displays

TCI Displays

TCI Evaluation

Overall preference
Ease of use
Pt. movement on incision
Time to eye-opening
Inaccuracies

- Limits: age 16-100 for conventional programs. Weight 30-150 kg
- Does not account for ethnopharmacology (cannot distinguish a Kenyan African from an Italian)
- Head injury
- Concomitant meds
- No problem:
  - Hypoalbuminemia
  - Rapid fluid admin

Pediatric use

- Kataria model can be used in children aged 3-16 yr and weighing 15-61 kg
- Paedfusor in children aged 1-16 yr and weighing 5–61 kg.
- Teenage children weighing > 61 kg can be managed using the Marsh adult model.

Use in obese

- There is a lack of evidence on whether it is better to use total body weight or another scalar such as adjusted body weight when using a TCI pump with these models in the obese. The Marsh and Schnider pharmacokinetic models and the calculated plasma propofol concentrations may not be accurate in the obese. When using TIVA in the obese, titration to clinical effect and pEEG monitoring is recommended.
- Society for Intravenous Anaesthesia (SIVA) Total Intravenous Anaesthesia 2017: guidelines for safe practice

Use in obese


And in the absence of TCI pumps in the USA...

TCI equipment- tiva manager

Practical application of TIVA

Select drugs to be used
Timing is everything- consider effect site peak and Co-induction
Higher index of vigilance for recall- reduce muscle relaxation, awareness monitor
Titrated infusions based on context-specific half-time

Don’t forget to bolus

Avoiding pitfalls in TIVA

- Use leur-lock connector, anti-reflux valve in IV tubing
- Keep it site in view when possible
- If infusion is disrupted due to dead battery, etc., do not start at previous target concentration (pump will deliver another loading dose)
- Careful when switching from inhaled to TIVA. Don’t forget to bolus propofol.

Drug combinations for TIVA
### Opioid infusion schemes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma Target Conc (ng/ml)</th>
<th>Bolus μg/kg</th>
<th>Infusion Rate μg/kg/min</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>1</td>
<td>1-3</td>
<td>0.02</td>
<td>Bal</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>0.03-0.1</td>
<td>N₂O/narc</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>40</td>
<td>10-20</td>
<td>0.25-1.0</td>
<td>Analg</td>
</tr>
<tr>
<td></td>
<td>160</td>
<td>80</td>
<td>1.0</td>
<td>Bal/N₂O</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.15</td>
<td>0.2</td>
<td>0.005</td>
<td>Bal</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>6</td>
<td>n/a</td>
<td>0.02</td>
<td>Analg</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.5-1</td>
<td>0.1-0.4</td>
<td>N₂O/narc</td>
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</table>

### Propofol context-sensitive dosing

- **Propofol only TIVA:** Induce 2-2.5mg/kg, then infuse:
  - 150-300 μg/kg/min first 10 minutes
  - 120-240 10 min to 2 hours
  - 75-150 beyond 2 hours
- **Propofol + opioid:** Induce 1.5-2mg/kg, then
  - 100-150 first 10 minutes
  - 90-140 10 min to 2 hours
  - 75-125 beyond 2 hours

### Ketamine infusion dosing

- **Induction:** 0.75-2mg/kg
- **Infusion 1-2 mg/kg/hr**
- **Midazolam 3-5 mg load, then 0.25 μg/kg/min**

**Pre-mixed maintenance infusion**

- 400 mg ketamine + 4mg midazolam in 100ml saline
- Infuse at 0.5 x weight in kg = ml/hr
- 2mg/kg/hr ketamine
- 0.33 μg/kg/min midazolam

### Propofol-Ketamine infusion

Extensive use in outpatient (office) settings with outstanding track record for safety and lack of side-effects.

- Mix ketamine 2mg/ml of propofol
  - Induce with 1-2mg/kg propofol in mixture
  - Give additional 0.5-1mg/kg ketamine after asleep
  - Infuse 140-200 μg/kg/min first 10 minutes (based on propofol)
  - 100-140 μg/kg/min for next 2 hours
  - 80-120 μg/kg/min after 2 hours

### Context-sensitive half-time

- Disopramide
- Thiopental
- Midazolam
- Ketamine
- Remifentanil
- Propofol

*Un Even Distribution*
Remifentanil Infusion

- Boon to all types of anesthesia
- Fast onset and recovery; independent of infusion duration
- Turn pump on at 1 μg/kg/min
  - Also start propofol bolus via pump, or wait 30 sec to inject
  - Maintain at 0.1-0.3 μg/kg/min for target plasma concentration of 5 ng/ml
  - Turn off 5-7 min before extubation. Extubate quickly upon awakening

Propofol-Alfentanil TIVA

- Induce
  - Propofol 0.5-1 mg/kg
  - Alfentanil 25-50 μg/kg
- Maintenance
  - Propofol 100-180 μg/kg/min
  - Alfentanil 0.5-2 μg/kg/min
  - Dosages loosely suggested; account for level of stimulation and concurrent meds (i.e., midazolam)

Dexmedetomidine

- dexmedetomidine 0.6 μg/kg with propofol 1.5 mg/kg, and lidocaine 1.5 mg/kg (induction/load)
- then Dex infusion at 0.3 ml/kg/hr with Lidocaine 2 mg/kg/hr
- Compared to remi-propofol, dex had better analgesia post-op (0-2 hours)

Bakan, M et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double blind study. Brazilian Journal of Anesthesiology. 2015; 65(3), Pages 191-199

Lidocaine

- Lido infusion 1.5 mg/kg/hr as anesthetic adjunct
- Reduced propofol 10% and sufenta 20%, without adverse effect on SSEP monitoring


Future of TIVA

Closed-loop anesthesia

Drug advances
- S+ ketamine enantiomer
- Propofol pro-drug
- New hypnotics (THRX-918661)

Non-invasive monitoring of propofol blood concentration

The Aneo TIVAS system

Summary

- TIVA techniques can provide numerous advantages over volatile-based anesthetics.
- While equipment set-up and cost is greater than using existing vaporizers, long-term savings can be appreciated.
- Context-sensitive PK considerations allow safe and effective narcotic dosing.
- Modern infusion technology and TCI lends control to IV techniques to rival vaporizer use.