Total Intravenous Anesthesia

A Rational Approach to Anesthetic Management

Michael Rieker, DNP, CRNA
Director, Nurse Anesthesia Program
Wake Forest Baptist Medical Center
Objectives

- Review drugs and methods in TIVA
- Discuss how propofol has aided 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 anesthesitics?

- 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)

- Volatiles assoc. with increased inflammation and decreased immune function
Optimal technique for neuroanesthesia

- Improved extent and duration of cerebral metabolic suppression.
- 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
Not a panacea

+ Titratable, but no diff in shivering, PONV, HTN.

- Wong AY. Eur J 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
Not a panacea

Pre-conditioning/tissue protection from volatiles is a nice side-effect.


No differences between TIVA and inhalational anesthesia groups with regard to duration of anesthesia, time to discharge from the PACU, bleeding, or incidence of adverse events.

- Vlessides, M. Anesthesiology News (07/01/12) Vol. 38, No. 7
Why infusions?

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

\(^1\)White PF. Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology. 59(4):294-300, 1983.
Why infusions?

- Avoid over and undershoot of dosage
- Avoid latency in reaching effect site
Over and undershoot of dosage

\[ y = 225x + 241 \]
\[ R^2 = 0.93 \]

\[ y = 274x + 46 \]
\[ R^2 = 0.92 \]

Latency in reaching effect site

Calculated blood and effect site (brain) concentrations following the bolus administration of propofol, 2.5 mg/kg over 60 seconds.

Latency in reaching effect site

Why infusions?

- Reduce workload intraoperatively
- Reduce total drug usage by 25-50%
Why infusions?

- More rapid awakening
- Less respiratory depression
Why infusions?

Discharge times reduced 30%

Patients met PACU discharge criteria 30 minutes faster with TIVA
Reliability of discharge improvement

Faster readiness, but discharge and cost savings are depending upon system

<table>
<thead>
<tr>
<th></th>
<th>TIVA Group (n = 25)</th>
<th>SF Group (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early recovery times (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye opening</td>
<td>5.0 ± 2.7</td>
<td>6.8 ± 3.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Response to commands</td>
<td>5.8 ± 3.0</td>
<td>7.2 ± 3.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Extubation</td>
<td>6.8 ± 3.2</td>
<td>7.8 ± 3.7</td>
<td>0.34</td>
</tr>
<tr>
<td>Orientation</td>
<td>7.4 ± 3.2</td>
<td>9.0 ± 3.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Time in OR after end of</td>
<td>10.3 ± 3.3</td>
<td>12.3 ± 4.3</td>
<td>0.08</td>
</tr>
<tr>
<td>surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldrete score ≥ 9</td>
<td>14.2 ± 7.7</td>
<td>14.2 ± 5.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Late recovery times (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PADSS ≥ 9</td>
<td><strong>103 ± 32</strong></td>
<td><strong>135.9 ± 51</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>Actual home discharge</td>
<td><strong>180.8 ± 38</strong></td>
<td><strong>192.8 ± 73</strong></td>
<td>0.47</td>
</tr>
</tbody>
</table>

### Why now?

#### Historical perspective

**Inhalation anesthesia**

<table>
<thead>
<tr>
<th>Good</th>
<th>open drop ether mask</th>
<th>Strength of pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>concentration-controlled vaporizers</td>
<td>Deliver MAC level</td>
</tr>
<tr>
<td>Best</td>
<td>RGM, neuro monitors</td>
<td>Titrate to effect-site concentration and response</td>
</tr>
</tbody>
</table>
### Why now?

#### Historical perspective

**Intravenous anesthesia**

<table>
<thead>
<tr>
<th>Good</th>
<th>IV bolus</th>
<th>Estimate time for recovery, based on $\beta t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>Infusion pump</td>
<td>Titrate according to context-specific half-time</td>
</tr>
<tr>
<td>Best</td>
<td>Rapid recovery drugs, target-controlled infusion pumps</td>
<td>Titrate to effect-site concentration and response</td>
</tr>
</tbody>
</table>
TIVA equipment
Propofol: wonder drug of the 90’s
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
Frequency of Side-Effects with Propofol

- Pain on Inj: 5.2
- N/V: 1.9
- Excitement: 1.3
- Hypotension: 1.1
- Brady: 0.4
- Pain: 0.3
- HTN: 0.3

McLeskey et. al. Anesth Analg 1993;77:S3-9
Reduced risk of postoperative vomiting

Meta-analysis of studies: propofol vs volatiles

Reduction in risk of vomiting after ‘Diprivan’ (induction and maintenance)


- All inhalational agents: 3.7
- Isoflurane (maintenance): 3.7
- Desflurane or sevoflurane (maintenance): 2.3

6 studies: p = 0.003
70 studies: p < 0.0001
42 studies: p < 0.0001
n = 4,074
Why now?

TIVA-TCI 2011
3rd World Congress of Total Intravenous Anaesthesia & Target Controlled Infusion
Singapore, 31 March - 2 April, 2011

Discover the Future of Safe Anaesthesia
www.kenes.com/tiva-tci
Specific indications for TIVA

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

- PONV similar between Propofol TIVA and Sevo + Dolasetron in high-risk patients. Late PONV was worse in TIVA group.

- PONV similar between TIVA without anti-emetic and volatile + anti-emetic
  - Paech *Anaesth Intensive Care* 30:153–9

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

- Volatile anesthetics inhibit natural killer cells and T lymphocytes.
- Volatiles also inhibit lymphocyte functions such as proliferation and cytokine production.
- Propofol and COX-2 inhibitors may deter tumor growth & metastasis.

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

<table>
<thead>
<tr>
<th>Good</th>
<th>IV bolus</th>
<th>Estimate time for recovery, based on $\beta t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>Infusion pump</td>
<td><strong>Titrate according to context-specific half-time</strong></td>
</tr>
<tr>
<td>Best</td>
<td>Rapid recovery drugs,</td>
<td><strong>Titrate to effect-site concentration and response</strong></td>
</tr>
</tbody>
</table>
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
Open three-compartment PK model
Context-sensitive half-time

Duration of a drug’s effects depends on way it’s administered

Context-sensitive half-time

Context-sensitive alterations in propofol kinetics

Context-sensitive half-time - Midaz.

Comparison of context-sensitive half-times for remimazolam and midazolam. Midazolam doses = 0.075 mg/kg/h; remimazolam doses ≥ 50 mg/h.

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>Thiopental</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>1.5</td>
<td>125</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Context-sensitive half life vs. necessary decrease

<table>
<thead>
<tr>
<th></th>
<th>Sufentanil ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance</strong></td>
<td></td>
</tr>
<tr>
<td>N₂O/Vapor</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>O₂/N₂O only</td>
<td>0.25-1.0</td>
</tr>
<tr>
<td>O₂ only</td>
<td>2-8</td>
</tr>
<tr>
<td>Ventilation</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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
TCI equipment
Key components of a TCI system

- Pharmacokinetics – a validated model with specific parameters for drug
- Algorithm(s) to control infusion rate
- “Control unit” i.e. software and microprocessors for above
- Infusion pump
- User interface for input of patient data and target blood concentration
Measured versus calculated blood propofol concentrations during ‘Diprifusor’ TCI administration of propofol in 46 patients.

Diprifusor

- Software program
- Commercially available ‘Diprifusor’ TCI systems:
  (a) Graseby 3500.
  (b) Vial Medical ‘Master TCI’
  (c) Alaris IVAC TIVA TCI
  (d) Terumo Terufusion® TE-372 TCI TIVA
Loading dose schemes by Diprifusor

Russell, D. Practical Aspects of Target-Controlled Infusion. *Anaesthesia Rounds* Oxfordshire, UK, TMG Healthcare Communications Ltd. P. 7
“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

Liquid Crystal Display (LCD)

- CALCULATED concentration
- TARGET concentration
- TCI status indicator
- TCI status indicators: ▲ the word CALCULATED and symbol ▼ blink during infusion
- Access INFO on effect-site (brain) concentration, time to target
- Access TOTAL amount of 'Diprivan' infused
- Small increment
- Small decrement

TCI Displays
TCI Displays

Graphical Liquid Crystal Display (LCD)

- Concentration \( \mu g/ml \)
- Decrement time (to predict time of awakening)
- Target concentration
- Effect-site concentration
- Time (minutes/hours)
- Current infusion rate
- Calculated concentration

Example:

- 10 min
- 2 \( \mu g/ml \)
- 0 h 00
- (324 ml/h)
- 35 min
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
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
- Titrate infusions based on context-specific half-time
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>3</td>
<td>0.20</td>
<td>Bal</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>0.70</td>
<td>N$_2$O/narc</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>40</td>
<td>20</td>
<td>0.25</td>
<td>Analg</td>
</tr>
<tr>
<td></td>
<td>160</td>
<td>80</td>
<td>1.0</td>
<td>Bal/N$_2$O</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.15</td>
<td>0.15</td>
<td>0.003</td>
<td>Bal</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td>0.01</td>
<td>N$_2$O/narc</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>6</td>
<td>1</td>
<td>0.02</td>
<td>analg</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1-2</td>
<td>0.4-1.0</td>
<td>N$_2$O/narc</td>
</tr>
</tbody>
</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: 0.75-2 mg/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 + 4 mg midazolam in 100 ml saline
  - Infuse at 0.5 x weight in kg = ml/hr
    - = 2 mg/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
Propofol-Ketamine infusion

Reeves JG, Glass PSA, Lubarsky DA, McEvoy MD. Intravenous nonopioid anesthetics. In Miller RD. Miller’s Anesthesia 6th ed. 2005
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 5ng/ml
  - Turn off 5-7 min before extubation. Extubate quickly upon awakening
Propofol-Alfentanil TIVA

**Induce**
- Propofol 0.5-1mg/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
Future of TIVA-Esterase Metabolism is in

- New hypnotics (THRX-918661/AZD3043)
- Methoxycarbonyl-etomidate
- Remimazolam- Sedation with a 6-mg initial loading dose, then 3-mg doses at >2-minute intervals. Recovery within 16 minutes for 89% of the treated population. Anesth & Analg. 2012 Aug;115(2):284-96.
Future of TIVA

- Closed-loop anesthesia
- Drug advances
  - S+ ketamine enantiomer
  - Propofol pro-drug
- Non-invasive monitoring of propofol blood concentration
Closed-Loop Coadministration of Propofol and Remifentanil Guided by Bispectral Index: A Randomized Multicenter Study

Ngai Liu, MD, PhD*, Thierry Chazot, MD*, Sophie Hamada, MD*, Alain Landais, MD†, Nathalie Boichut, MD‡, Corinne Dusaussoy, MDS, Bernard Trillat, MScII, Laurent Beydon, MDS, Emmanuel Samain, MD¶, Daniel J. Sessler, MD¶ and Marc Fischler, MD*
It’s all getting so easy, but maybe too easy?

CAPS Device for Propofol Sedation Demonstrates Nurse Confidence and Ease of Use

06/11/2007

BALTIMORE — A computer-assisted personalized sedation (CAPS) device is being tested to determine whether it could provide physician/nurse teams with an on-label means of confidently administering propofol sedation for routine gastrointestinal endoscopy (EGD) and colonoscopy procedures. The feasibility study, completed last year, was presented at the Society of Gastroenterology Nurses and Associates (SGNA) Annual Meeting by Claudia Yitzman, RN, CRC, in a presentation entitled, “Computer-Assisted Personalized Sedation (CAPS) for GI Endoscopy: Nursing Implications and Patient Satisfaction.” The SGNA meeting was held in Baltimore from May 19-24.

Results of the feasibility study demonstrated the ability of the device to facilitate the administration of minimal to moderate propofol sedation appropriate to individual patient needs, while achieving high clinician and patient satisfaction, and rapid recovery times. None of the patients required the assistance of manual or mechanical ventilation during the procedures, and no device-related adverse events were reported. The U.S. study included 24 subjects undergoing elective endoscopy (12 colonoscopy and 12 EGD).

As the assistant to the endoscopist in the feasibility study, the nurse was comfortable using the device to administer propofol sedation and assess subjects. Overall, the nurse found the investigational CAPS device intuitive and user-friendly, leading to a short learning curve. The closing limits and the automated response algorithms built into this CAPS device gave the team confidence that the system could be used to maintain an appropriate level of sedation for each patient throughout the procedure. Subjects were calm, comfortable and cooperative, all procedures were successfully completed, and recovery occurred on average in 25 seconds.
FDA Grants Premarket Approval For The SEDASYS

May 3, 2013
- initiation and maintenance of minimal-to-moderate sedation
- ASA physical status I and II patients ≥ 18 years old
- colonoscopy and EGD
- introduced on a limited basis beginning in 2014
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.
- More info: UK Society for Intravenous Anaesthesia
  www.sivauk.org