Total Intravenous Anesthesia:

A Rational Approach to Anesthetic Management

Michael Rieker, DNP, CRNA
Director, Nurse Anesthesia Program
Wake Forest University 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.

Drug administration

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
- Better preservation of cerebral autoregulation vs. volatile
  - Ishikawa, Masui. 2003;52(4):370-7
  - McCulloch Anesthesiology. 2007;106(1):56-64
- Reduced stress response.

Advantages of TIVA over balanced

- Improved surgical field (bleeding)
- Volatiles assoc. with inc. inflammation and dec. immune function
  - Ken PH. BIS lecture.
- Improved CPP, less interference with SSEP, MEP, AEP: Minimal post-op side-effects; potential neuroprotective effects via antioxidant properties.

Not a panacea

- + Titratable, but no diff in shivering, PONV, HTN.
  - Wong AY. Eur J Anaesth 2006;23(7):586-90
- Cost. (But less PONV)
  - Rohm KD. Acta Anaesthesiologica Scandinavica. 2006;50(1):14-8

Propofol: wonder drug of the 90’s

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

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>Agents</th>
<th>All</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>2.3</td>
<td>3.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Frequency of Side-Effects with Propofol

<table>
<thead>
<tr>
<th>Side-Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on Inj</td>
<td>5.2</td>
</tr>
<tr>
<td>N/V</td>
<td>1.9</td>
</tr>
<tr>
<td>Excitement</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1.1</td>
</tr>
<tr>
<td>Brady</td>
<td>0.4</td>
</tr>
<tr>
<td>Pain</td>
<td>0.3</td>
</tr>
<tr>
<td>HTN</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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%

McLeskey et al. Anesth Analg 1993;77:S3-9

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

Why infusions?

Discharge times reduced 30%

Patients met PACU discharge criteria 30 minutes faster with TIVA


Why now?

Historical perspective

Inhalation anesthesia

Good
Better
Best

open drop ether mask
concentration-controlled vaporizers
RGM, neuro monitors

Strength of pulse
Deliver MAC level
Titrate to effect-site concentration and response

Intravenous anesthesia

Good
Better
Best

IV bolus
Infusion pump
Rapid recovery drugs, target-controlled infusion pumps

Estimate time for recovery, based on $\beta_{1/2}$
Titrate according to context-specific half-time
Titrate to effect-site concentration and response

Why now?

Reliability of discharge improvement

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


Why now?

TIVA equipment
Why now?

- 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.
  - White, British Journal of Anaesthesia 98(4):470-6, 2007
- PONV similar between TIVA without anti-emetic and volatile + anti-emetic
  - Paech Anesth Intensive Care 30:153–9
- 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

<table>
<thead>
<tr>
<th>Good</th>
<th>IV bolus</th>
<th>Estimate time for recovery, based on βt1/2</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>

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 alterations in propofol kinetics


Key effect site concentration levels

<table>
<thead>
<tr>
<th>Induction and Intubation</th>
<th>Fentanyl</th>
<th>Alfentanil</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>3-5 ng/ml</td>
<td>250-400</td>
<td>0.4-0.6</td>
</tr>
<tr>
<td>(O_2/N_2O) only</td>
<td>8-10</td>
<td>400-750</td>
<td>0.8-1.2</td>
</tr>
</tbody>
</table>

Maintenance

| \(N_2O/Vapor\)          | 1.5-4   | 100-300   | 0.25-0.5   |
| \(O_2/N_2O\) only       | 1.5-10  | 100-750   | 0.25-1.0   |
| \(O_2\) only            | 15-60   | 1000-4000 | 2-8        |

Adequate Ventilation

| 1.5 | 125 | 0.25 |
Context-sensitive half life vs. necessary decrease

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>Sufentanil ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance</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>0.5-1.0</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.

Variants of TCI terminology

- CATIA - Computer Assisted Total Intravenous Anaesthesia
- TIAC - Titration of Intravenous Agents by Computer
- CACI - Computer Assisted Continuous Infusion
- CCIP - Computer Controlled Infusion Pump

TCI equipment

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**

**TCI Evaluation**

**Inaccuracies**

- Limits: age 16-100 for conventional programs.
- Weight 30-150 kg
- Does not account for ethnomedication (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

**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_{0}/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>N_{0}/narc</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_{0}/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_{0}/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 µg/kg/min 10 min to 2 hours
  - 75-150 µg/kg/min beyond 2 hours
- **Propofol + opioid**: Induce 1.5-2mg/kg, then
  - 100-150 µg/kg/min first 10 minutes
  - 90-140 µg/kg/min 10 min to 2 hours
  - 75-125 µg/kg/min 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

**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**

- Closed-loop anesthesia
- Drug advances
  - S+ ketamine enantiomer
  - Propofol pro-drug
  - New hypnotics (THRX-918661)
- Non-invasive monitoring of propofol blood concentration
It's all getting so easy, but maybe too easy?

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.
- More info: UK Society for Intravenous Anaesthesia www.sivauk.org