TIVA and Smart Pumps: TCI systems

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TCI: What is it

- Target Controlled Infusion system: Infusion pump system

- Allows targeting a fixed plasma concentration of an iv drug to achieve and maintain a desired level of anesthetic effect

- Made in USA
  - Foundations
  - Software applications
  - Publications

- Available all over the world
  - Exception: USA (civilian)
    - TARGIT Initiative from the US Army
  - Strict FDA regulations (~1995)
TCI system: What it does?

- Administers iv drug to achieve a target concentration
  - Plasma (Cp)
  - Effect site (Ce)
- To achieve, maintain and rapidly change a desired level of anesthetic effect in response to demands
- Predictions based on models of drug effect
- A “change of paradigm” required:
  - mL/h >> mcg/mL
  - Speed of infusion >> target concentrations

Alfentanil: bolus vs TCI

![Graphs comparing bolus and TCI schemes for Alfentanil](image)
Anesthetic State

Hypnosis

Stable Homeostasis

Immobility

Analgesia

TCI system: Stable effect

- Continuous infusion of propofol or fentanyl
  - Slow to reach stable effects (steady state)
  - Very slow reaction to change
- Inhalation anesthetics
  - Open vaporizer
  - Over pressure

TCI: PKPD Model
1. Instead of estimating the concentration based on dosing
2. Anesthesiologist sets Target Conc
3. The TCI system automatically
   1. Estimate speed of infusion
   2. Update it every 10 sec
   3. Compensate for
      1. Elimination
      2. Distribution

TCI: objectives

- Reach the desired target of effect
- As soon as possible
- Only during the time required
- Anticipating changes in intensity

The Model

Pharmacokinetics-Pharmacodynamics (PKPD)

Stanpump
- RUGLOOP
- Diprifusor
- Base Primea (Fresenius)
- AsenaPK (Alaris)
- Syramed TCI (Arcomed)
- Braun Systems
Pharmacokinetic (PK) Model

- Parameters
  - A, B, C
  - L1, l2, l3
- Define the characteristics of each drug
  - Distribution to tissues
  - Elimination from body
  - Onset and offset of effect

The BET scheme

- Bolus filling up central compartment
- Continuous Infusion:
  - Compensates Elimination
  - Compensates for Transfer to tissues
- How?:

\[ Maintenance \ Infusion\ (t) = C_T \times (k_{10} + k_{12}e^{-k_{21}t} + k_{31}e^{-k_{31}t}) \]

Krüger-Thiemer 1968

PK Study: bolus

 Concentration [ng/mL] vs. Time [min]

\[ Cp = A \cdot e^{-l_1t} + B \cdot e^{-l_2t} + C \cdot e^{-l_3t} \]

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Krüger-Thiemer 1968
TCI systems: Information

- $C_T$: Target concentration
- $C_p$: Estimated plasma concentration
- $C_e$: Estimated effect-site concentration
- Time to achieve new target
- Integrated with effect measures:
  - NMB, EEG, MLAEP, hemodynamics, $pCO_2$, ...

PKPD Models

- **Propofol**
  - Schnider (PKPD)
  - Marsh (PK)
  - Kataria (PK, Pediatrics)
  - Barr (PKPD, ICU patients)
  - Morbidly Obese
    - Cortinez (PK)
    - Van Kralingen (PKPD)

- **Remifentanil**
  - Minto (PKPD)
  - Age
  - Weight
  - Height
  - Gender

- **Alfentanil (Scott)**
- **Rocuronium**
- **Research protocol (Stanpump allows any iv drug)**

Fresenius Kabi Base Primea®

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Careful in special populations: aged, cardiac, sepsis, shock, ...
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Before selecting a model learn about its characteristics

TCI systems:

**Precision**

- Innacurary (MDAPE) around 20-30%

**Bias (MDPE)**

Glass et al.
Miller’s Anesthesia, 6th edition
Chapter 12

Therapeutic Intervals: Remifentanil

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>Cp50 for tracheal intubation with 70% N2O</td>
<td>Glass Anesth 79 (1993)</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Cp50 for skin incision with 70% N2O</td>
<td>Glass Anesth 79 (1993)</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Cp50 for skin closure with 70% N2O</td>
<td>Glass Anesth 79 (1993)</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Cp50 for tracheal intubation with 100% O2</td>
<td>Glass Anesth 79 (1993)</td>
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<tr>
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<td>Cp50 for skin incision with 100% O2</td>
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<td>Cp50 for skin closure with 100% O2</td>
<td>Glass Anesth 79 (1993)</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Isoflurane 50% MAC reduction</td>
<td>Kapila Anesth 81 (1994)</td>
</tr>
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Clinical Application

Sedation-Analgesia
TCI systems: Clinical Applications

- Any kind of setting:
  - Ambulatory
  - In-patient
- Any kind of surgery:
  - General: open, laparoscopy
  - Neurosurgery
  - Thoracic
- Any kind of general anesthesia:
  - Total i.v.
  - Inhalation + opioid TCI
  - LMA or Intubation

• Sedation-Analgesia (MAC-Sedation)
  - Spinal or epidural
  - Peripheral blocks
  - GI Endoscopy or any other procedural sedation

• Sedation in Critical Care

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  - Spinal
  - Peripheral blocks
  - GI Endoscopy and other procedural sedation

• N~110 (+70) patients
• Multiple PRO-REMI target combinations
• Measured different effects
TCI: setting up the system

FreseniusKabi Base Primea®

Time from start of infusion [25 msec]
**Propofol-Remifentanil effect data**

- Data from 110 patients
- >10,000 data points
- Expressed here as colored cubes
- Estimate the surface of relation
- Define “target concentrations” of propofol and remifentanil (combined)
- For a given effect
- Prospectively validated

**RSS4**

**[Arousable to tactile stimuli]**

<table>
<thead>
<tr>
<th>Propofol (µg·mL⁻¹)</th>
<th>Remifentanil (ng·mL⁻¹)</th>
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<tbody>
<tr>
<td>2.7–1.8</td>
<td>0–1.5</td>
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<tr>
<th>AAI/2</th>
<th>BIS</th>
<th>IoC</th>
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<tr>
<td>25–30</td>
<td>71–75</td>
<td>72–76</td>
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These combinations can be used as safe starting points when using TCI systems to provide MAC-sedation for GI endoscopy (ultrasonographic endoscopy, ERCP, ...)

Gambús P; Anesth & Analg, 2011
Conclusions

- TCI is the optimal system to administer iv drugs
- Allows targeting fixed concentration
- To achieve, maintain and rapidly change a desired level of anesthetic effect in response to demands
- As fast as possible and only during the time needed
- Less variability than bolus or continuous infusion
  - It is adjusted to age, weight, height, gender of patients

Conclusions

- Anesthesiologist must have “different” knowledge on the iv drugs to use: Concentrations
- Choose a PKPD model:
  - That better adjusts to patient: covariate factors
  - Prospectively validated, accurate and unbiased
- Select targets according to evidence
  - Therapeutic intervals:
    - Patient characteristics (genetics?)
    - Intensity of stimuli
- Titrate to effect: hypnosis, NMB
  - and to avoid side effects
- As usual be careful with old, sick patients
  - start with low targets and small increases