Models for Inhalant and Intravenous Drugs

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Everything profitable I ever invented is owned by Brigham and Woman’s Hospital (Edwards Vigilance CCO, Baxter InfusOR Pump, Master-Medical Instant Timer, CareFusion-Cardinal-Alaris-IVAC-Signature Pump, Perkin-Elmer Life Watch™ CO₂ Monitor
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In 2005
I had I have performed funded research on Sevoflurane, Desflurane, Isoflurane
I was a frequent speaker for Baxter and occasional speaker for Abbott
I had a financial interest in Gas Man® and Med Man Simulations, Inc. - I made no profit
in 1997 Gas Man® and Med Man Simulations, Inc. became a 501(C)(3) charitable organization
Models for Inhalant and Intravenous Drugs
IV and Inhalant Differences

Pharmacological
Receptor-directed
No (known) receptor

Physiological
Effect-directed
Multifaceted
IV and **Inhalant** Kinetic Differences

Different Models
Different Authors
Different Speakers
Different Units of Measure
Different weeks at BWH
Shafer last week, me this week
Same Group of Clinical Users
IV Model

Entry via a *vein*
Distribute to *central volume of distribution*
Sample *arterial concentration* after 5 min
Model and estimate and control *effect site*
Model *ignores* cardiac output
Measure concentration in art. or ven. *blood*
Measurements are *difficult and uncommon*
Tissue and blood concentrations are *not equal*
*Dosing* is sometimes *confusing*
Inhalant Model

Entry via *Lungs*

Cardiac output affects blood level

*Tension* (AKA Partial Pressure) measures *gas, blood, and tissue* levels

We ignore *concentrations* whenever possible

*Blood/Gas Solubility Dominates kinetics*

Expired (Exp) tension is *measured* commonly

*Exp* tension estimates *blood* tension *now*

Tissue and blood *tensions become equal w time*

VRG (brain) lags blood by *2-3 minutes* ($\tau$)
Major difference between Inhalant and IV

Inhalant measure is tension or partial pressure
  Maximum tension anywhere is vaporizer setting
  Maximum tension in alveolar gas is inspired tension
  Maximum tension in brain is alveolar tension

IV measure is plasma concentration
  No maximum
    A small Central Compartment results in high concentration
Actual Volume and Concentration are difficult to compute
Trial dosage is based on body weight, possibly to some power
$Wt^{0.75}$
Inhaled Kinetic Model
Compartments and Paths
Inhaled Kinetic Model
Conductance move drug from place to place

Compartments and Paths

- **Vaporizer**
- **Breathing Circuit**
- **Lungs**
- **Arterial Blood**
- **Tissues (Brain)**
- **Venous Blood**

FGF = Fresh Gas Flow

CO = Cardiac Output

VA = Alveolar Ventilation
Inhaled Kinetic Model
Measurements confirm model and control care

Compartments and Paths
- Setting
- Inhaled Gas
- Exhaled Gas
- Anesthetic Depth
- Vaporizer
- Breathing Circuit
- Lungs
- Arterial Blood
- Tissues (Brain)
- Venous Blood

Conductances
- FGF = Fresh Gas Flow
- CO = Cardiac Output
- VA = Alveolar Ventilation
The Model - Compartments and Flows

The diagram illustrates the flow of gases and substances through various compartments of the body, including the vaporizer, breathing circuit, lungs, blood, tissues, and venous blood. The model includes components such as fresh gas flow (FGF), alveolar (Lung) vent, cardiac output, and venous blood flow. The diagram also shows the weight (70 Kg) and agent (Sevoflurane) used in the simulation.
The Model - Return Flows

Breathing Circuit

Lungs

Venous Blood

Agent: Sevoflurane
Circuit: Semi-Closed
Weight (Kg): 70

DEL % atm: 8.0

CKT: 0.0
ALV: 0.0
ART: 0.0
VRG: 0.0
MUS: 0.0
FAT: 0.0
VEN: 0.0

Time (h:mm:ss): 0:00:00

Uptake (L) ($): 0.00
Delivered (L) ($): 0.00

Speed: 60x

FGF L/m: 8.00
VA L/m: 4.00
CO L/m: 5.00

Begin
The Model - From Vaporizer to Brain!

Vaporizer

Brain (VRG)

Agent: Sevoflurane
Weight (Kg): 70
Circuit: Semi-Closed

DEL % atm: 8.0
CKT: 0.0
ALV: 0.0
ART: 0.0
VRG: 0.0
MUS: 0.0
FAT: 0.0
VEN: 0.0

FGF L/m: 8.00
VA L/m: 4.00
CO L/m: 5.00

Time (h:mm:ss): 0:00:00
Uptake (L): 0.0
Delivered (L): 0.0
Speed: 60x

Begin
Measurements we make

Breathing Circuit

Vaporizer

Setting

Brain EEG, BIS, PSI?

HR, BP

Agent: Sevoflurane

Weight (Kg): 70

Circuit: Semi-Closed

DEL %atm: 8.0

CKT: 0.0

ALV: 0.0

ART: 0.0

VRG: 0.0

MUS: 0.0

FAT: 0.0

VEN: 0.0

FGF L/m: 8.0

VA L/m: 4.0

CO L/m: 5.0

Time (h:mm:ss): 0:00:00

Uptake (L): 0.0

Delivered (L): 0.0

Speed: 60x
Time, Uptake, and Delivered Liters and $

Questions on Model?
Gas Man® Model and Math are correct.

Thus, we can use them.

- (A) Wash-in 360 minutes = 6 hr 15 minutes
- (B) Wash-out after breathing 1 MAC for 1 hr.
- (C) Wash-out after breathing 1 MAC for 2 h.
- (D) Wash-out after breathing 1 MAC for 4 h.
- (E) Washout after breathing 1 MAC for 12 h.

In a multi-compartment System

Intelligent drug administration can achieve the desired effect

Intelligence, here, means

Know drug kinetics

Movement of drug through compartments

Know drug dynamics

Dose-response relationship at effect site
IV Drug Administration to achieve and maintain constant effect

One compartment with no loss

Bolus

Actually would last forever!
Bolus fills a sealed compartment

Experiment

Volatile
Liquid
Agent
Bolus fills a sealed compartment

Experiment

Volatile
Liquid
Agent

V
Bolus fills a sealed compartment

Experiment

Volatile
Liquid
Agent
Gas Man example

Bolus into breathing circuit
No removal (FGF = 0, VA = 0)
Removal via alveolar ventilation (VA)
0.5 mL Liquid injection
Conc = \(0.5 \times \frac{189 \text{ mL Vap}}{6000 \text{ mL ckt}}\)
\[= 0.01575 = 1.6\%\]
Ventilate from ckt to lungs
IV Drug Administration

to achieve and maintain constant effect

One compartment with no loss
Bolus

One compartment real system (w clearance)
Bolus + constant infusion

Two compartment system
Bolus + constant + exponential decrease

Three Compartment system
Bolus + constant + 2 exponential decrease

Complicated mathematics
Open Loop Control based on “population-based parameters”
By hand or by Computer
IV Drug Administration to achieve and maintain constant effect

Closed-loop control
Based on some measurement
CV Effects
Estimate from EEG
Other
Step response causes the curve we are familiar with:

- Initial rise
- Plateau
- Knee
- Tail
Step response for many agents from Ether to Xenon
Step response for many agents from Ether to Xenon

October 16, 1846
Agents with a new spin

MatLab Simulation of
Creation and rotation of
Continuous distribution of Lambda and Alveolar Tension curve with Plateau

Up and Down Bolus are both possible with Inhaled Drugs

Up Bolus - Induces anesthesia quickly
  Typical 50 seconds
  Well tolerated by adults without premedication
  Fast from high inspired concentration
  Fast from one or more deep breaths
Up Bolus deepens existing anesthesia quickly
Special advantages of inhalation route

Breathed in via lungs
  100% of cardiac output interacts
Still distributed, like IV Drugs
Breathed out via lungs
  100% of cardiac output allows high clearance
    Low Blood/Gas Solubility creates high clearance
End-expired level ≈ Alveolar ≈ Blood
Brain + CV follow blood with ≈ 3 minute delay
End-expired agent monitor

Agent Monitor monitors
End-tidal agent

Cardiovascular Monitor monitors HR, BP,...

Models predict and help to interpret
Alveolar, Blood, Brain, Other tissues

Gas Man® is my model
Inhalants are fast in achieving control

“An inhalation bolus of sevoflurane seems to be more effective than an IV remifentanil bolus during maintenance, with more effective control of hemodynamic responses to surgical stress.”

Bolus up
Bolus down, then up
Adjust DEL for 1 MAC, Overlay FGF

8 -> 4 -> 2 -> 1 LPM
Adjust DEL for 1 MAC, Overlay FGF

Legend
- 55sevo 8 LPM Const MAC Brain
- 65sevo 4 LPM Const MAC Brain
- 75sevo 2 LPM Const MAC Brain
- 85sevo 11 LPM Const MAC Brain

- DEL
- CKT
- ALV
- VRG
- MUS
- FAT
- VEN
- MAC

- 55sevo 8 LPM Const MAC Brain
- 65sevo 4 LPM Const MAC Brain
- 75sevo 2 LPM Const MAC Brain
- 85sevo 1 LPM Const MAC Brain

Help
Close
Low Flow

- Reduces Cost
- Reduces Control
Bolus Techniques

- Bolus Up
  - IV Drugs
  - Inhaled Drugs

- Bolus Down
  - Inhaled Drugs only
Agent Monitors Show and Teach

• Inhalation anesthesia kinetics

• How to better administer anesthetics
• How to predict the result of anesthetic administration

• Graphic Trends facilitate this understanding.
• They show the time course of anesthesia
• This is more important than static numerals

• Gas Man® first
Single Breath Induction

• Bolus up followed by bolus down
• Fast induction
• Avoid overdose once airway is secured
• Agent Monitor and Gas Man® graphs show this
Gas Man® shows
Single Breath Induction
Gas Man® shows Single Breath Induction
Superimpose

Gas

Man®

Graph

Agent

Monitor

Graph

Sevo
These Trend Graphs show all variables: Bolus up and down
Enough of going to sleep

It’s now time to

Wake Up!

!
Gas Man® Correctly predicts Emergence Time

- **(A)** Wash-in
  360 minutes = 6 hr
  15 minutes

- **(B)** Wash-out
  after breathing
  1 MAC for 1 hr.

- **(C)** Wash-out
  after breathing
  1 MAC for 2 h.

- **(D)** Wash-out
  after breathing
  1 MAC for 4 h.

- **(E)** Washout
  after breathing
  1 MAC for 12 h.

Gas Man® shows Emergence Time

Gas Man Simulation
Gas Man® shows
Emergence Time
Gas Man® Overlays
Compare Emergence with Iso, Sevo, Des

Legend:
- Des 1 L 18pc 87 pc (Desflurane)
- Sev 4 L 8pc 2 L (Sevoflurane)
- 10 hr Iso (Isoflurane)
Gas Man® Overlays
Compare Emergence with Iso, Sevo, Des

Legend
Des 1 L 18pc 8 7 pc (Desflurane)
Sev 4 L 8pc 2 L (Sevoflurane)
10 hr Iso (Isoflurane)

Awake
0.33 MAC
In Brain

ALV
VRG
At lower value, time difference is greater.

Legend:

Des 1 L 18pc 8 7 pc (Desflurane)
Sev 4 L 8pc 2 L (Sevoflurane)
10 hr Iso (Isoflurane)
Residents show emergence times on Ambulatory Anesthesia Rotation
Gas Man Comparison - September

1 MAC brain  Iso, Sevo, Des for 1.5 hours
Use the same FGF, VA and CO for all drugs
Start with higher flows for the first few minutes
Perform a Wake up comparison
Measure time for VRG to reach 0.33 MAC
Measure time for VRG to reach 0.2 MAC
Here, Gas Man simulations are inserted into PowerPoint
Overlay of three wake ups 0.33 MAC

Legend

Des 1.5 hr 2L gas (Desflurane)
Sev 1.5 hr 2L gas (Sevoflurane)
Iso 1.5 hr 2L gas (Isoflurane)
Overlay of three wake ups 0.33 MAC

Time to 0.33 MAC:
- 05' 26”
- 07’ 42”
- 10’ 55”

Legend:
- Des 1.5 hr 2L gas (Desflurane)
- Sev 1.5 hr 2L gas (Sevoflurane)
- Iso 1.5 hr 2L gas (Isoflurane)
Overlay at 0.2 MAC

Legend

Des 1.5 hr 2Lgas (Desflurane)

Sev 1.5 hr 2Lgas (Sevoflurane)

Iso 1.5 hr 2Lgas (Isoflurane)
Overlay at 0.2 MAC

Legend:
- Des 1.5 hr 2L gas (Desflurane)
- Sev 1.5 hr 2L gas (Sevoflurane)
- Iso 1.5 hr 2L gas (Isoflurane)

Time to 0.20 MAC:
- 07’ 25”
- 11’ 26”
- 17’ 45”
Overlay at 0.2 MAC

Time to 0.20 MAC

Time to 0.33 MAC

Legend

Des 1.5 hr 2L gas (Desflurane)

Sev 1.5 hr 2L gas (Sevoflurane)

Iso 1.5 hr 2L gas ( Isoflurane)
These simulations are similar to


Except,
Our residents used Gas Man® on their own
Eger EI, Shafer SL. Context-Sensitive Decrement Times for Inhaled Anesthetics. Anesth Analg 2005 101: 688-696 (Tutorial). [Figure 1]
Journal Club week before this lecture


Authors used Gas® Man to infer much about inhalation anesthesia and different drugs

David Goodman Compared Emergence after
Isoflurane 1 hr
Sevoflurane 4 hr
Desflurane 4 hr
Cases 4 hrs Sevo, Des, 1 hr Iso

Legend:

- des 4 hr constant take 2 (Desflurane)
- iso 1 hr constant mac take 2 (Isoflurane)
- sevo 4 hrs constant mac vrg
Observe wake up

Legend

- des 4 hr constant take 2 (Desflurane)
- iso 1 hr constant mac take 2 (Isoflurane)
- sevo 4 hrs constant mac, vrg
Wake up from Iso 1 hr is inferior to Sevo or Des for 4 hrs. Wake up from 4 hr Des is superior to 4 hr Sevo.
Eger & Shafer published this, Sept 2005

BWH Residents do similar work as homework assignments

We all use the same Gas Man® model

Eger EI, Shafer SL. Context-Sensitive Decrement Times for Inhaled Anesthetics. Anesth Analg 2005 101: 688-696 (Tutorial). [Figure 1]
Importance of Solubility

Blood

Brain

Muscle

Fat

Show Gas Man® Results
Anesthetics in Fat builds up very slowly

Important in bariatric patients
Switching Agents is confusing
Switching Agents doesn’t work

• Confuses the Agent Monitor
  Difficult to measure two agents simultaneously
  Difficult to add their effects
  Difficult to graph their cumulative trend

• Confuses the Clinician
  Difficult to know the time required for change
  Difficult to know what FGF is required for change

• Fresh Gas Flow affects time course
  High Flow fast
  Low Flow slow

• Sevo -> Iso -> Sevo doesn’t save much money

• Sevo -> Des after airway control to allow very low FGF

Gas Man® Example
Philip JH. Inspired Sevoflurane Remains After Switching to Desflurane with 2 L/min FGF. Anesthesiology 2000 (Abstract)
Thank you