Inhalational Anesthesia in the Pediatric ICU

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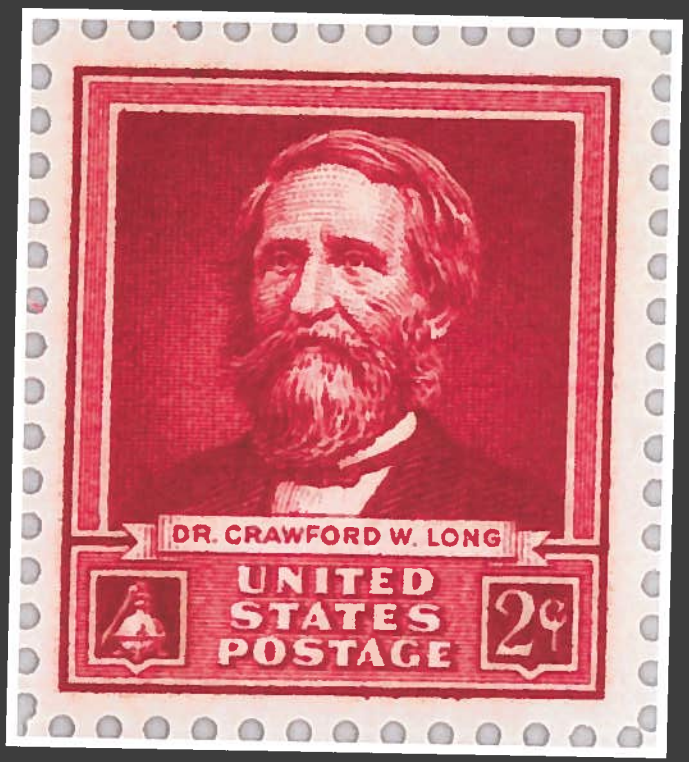
Inhalational Anesthesia

- ***history***
- chemical structure & physical properties
- metabolism & interactions
- end-organ effects
- clinical applications
- delivery in the ICU

Crawford Long

- born in 1815 in Danielsville, Georgia
- MD degree from University of Pennsylvania in 1839
- studied surgery in New York
- practiced medicine in Georgia
- anesthetized patient with an ether soaked towel
  - March 30, 1842
- also used ether in obstetrical cases


DR. CRAWFORD W. LONG
UNITED
STATES
POSTAGE
2¢

William Thomas Green Morton

- originally a dentist
- later went to medical school
  - wife's parents did not approve of his profession
- September 30, 1846 – ether for tooth extraction
- October 16, 1846 – neck tumor
  - first public display of ether use

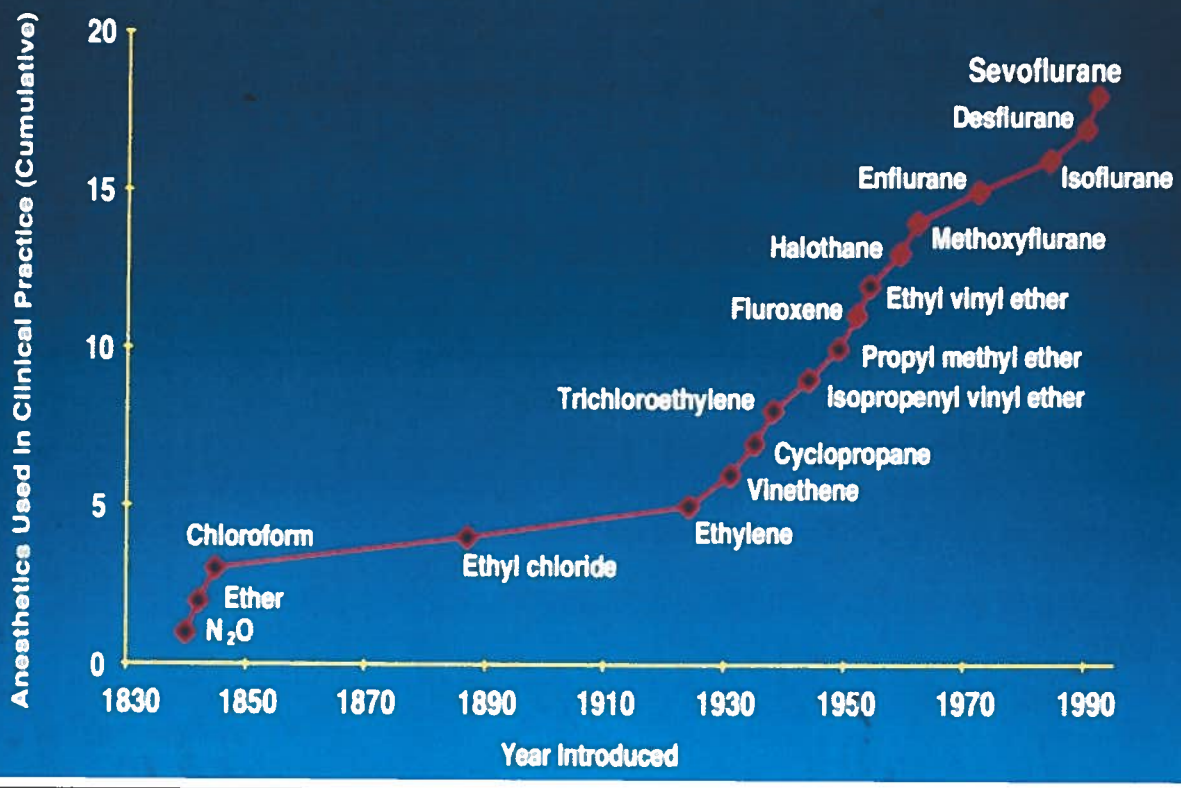
History of Inhalational Anesthesia

- nitrous oxide
  - lack of potency
- ether and chloroform
  - flammable + adverse physiologic effects
- 1940's
  - advances in physical chemistry due to nuclear program
- trichlorethylene
  - hepatotoxicity, neurotoxicity, delayed awakening

Fluorinated Agents

- fluroxene (2,2,2,-trifluoroethyl vinyl ether)
  - first fluorinated hydrocarbon
  - introduced into clinical practice in 1951
  - arrhythmias, nausea/vomiting, hepatotoxicity
- halothane
  - introduced into clinical practice in 1956

History of Inhalation Anesthetics



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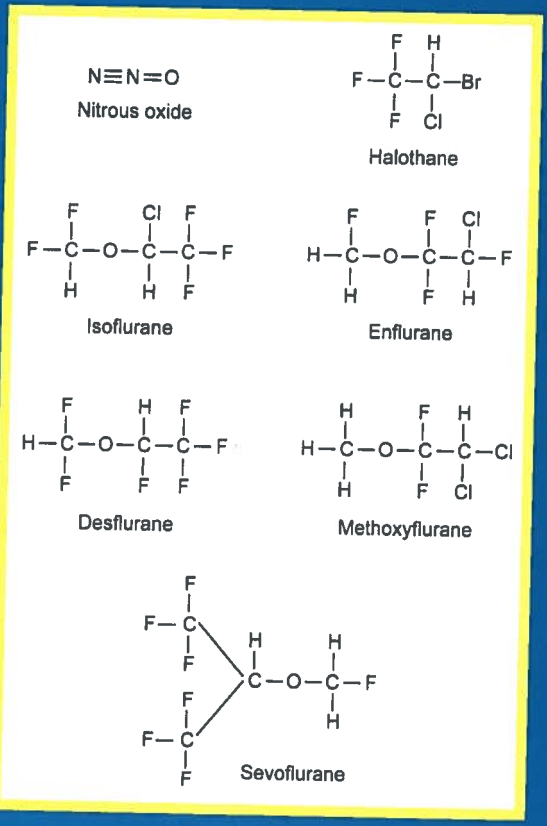
Inhalational Anesthesia

- alkanes
  - halothane
  - chloroform
- ethers
  - methyl-ethyl ethers
    - isoflurane
    - enflurane
    - desflurane
  - methyl-isopropyl ether
    - sevoflurane



Alkanes: Issues

- cardiovascular depression
- arrhythmias
- hepatotoxicity

Inhalational Anesthetic Agents: Differences

- potency (MAC)
- cardiovascular effects
- metabolism
  - fluoride
  - TFA or HFIP
- solubility
  - gas (blood:gas partition coefficient)
  - fat (blood:oil partition coefficient)

Minimum Alveolar Concentration

- MAC
- used to judge the potency of the agent
- expressed as percentage
- alveolar concentration at which 50% of subjects do not move in response to surgical incision
- lower MAC = higher potency
- modified by several factors

Vapor Pressure

- volatile liquids
  - transform into gas or vapor
- vapor pressure
  - potential to form a gas or vapor
- administered by a vaporizer
  - agent specific
  - variable bypass
  - key index filling system

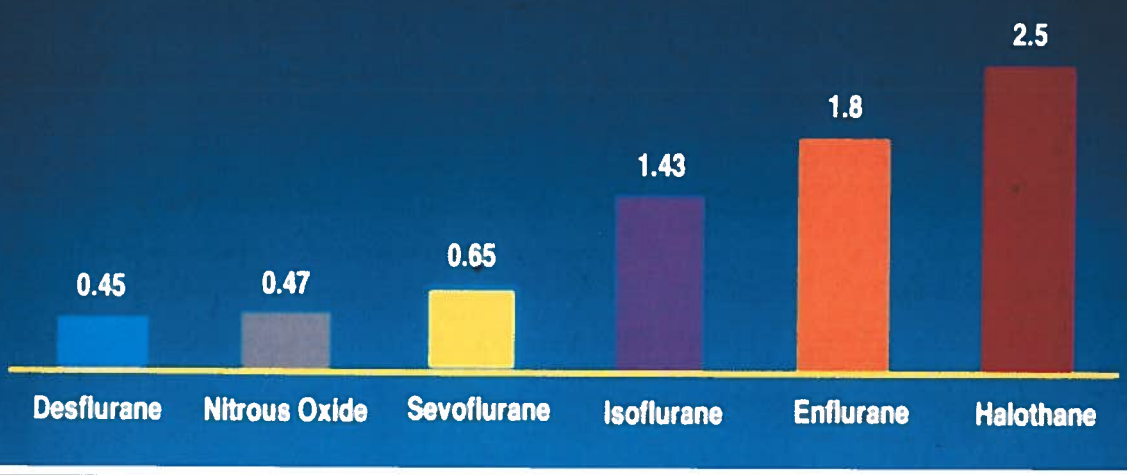
Inhalational Anesthesia

Agent	Vapor pressure (mmHg at 20°C)	Blood:Gas partition coefficient	MAC (%)
Halothane	243	2.54	0.76
Enflurane	175	1.91	1.7
Isoflurane	238	1.46	1.2
Sevoflurane	160	0.69	2.0-2.3
Desflurane	664	0.42	6.0

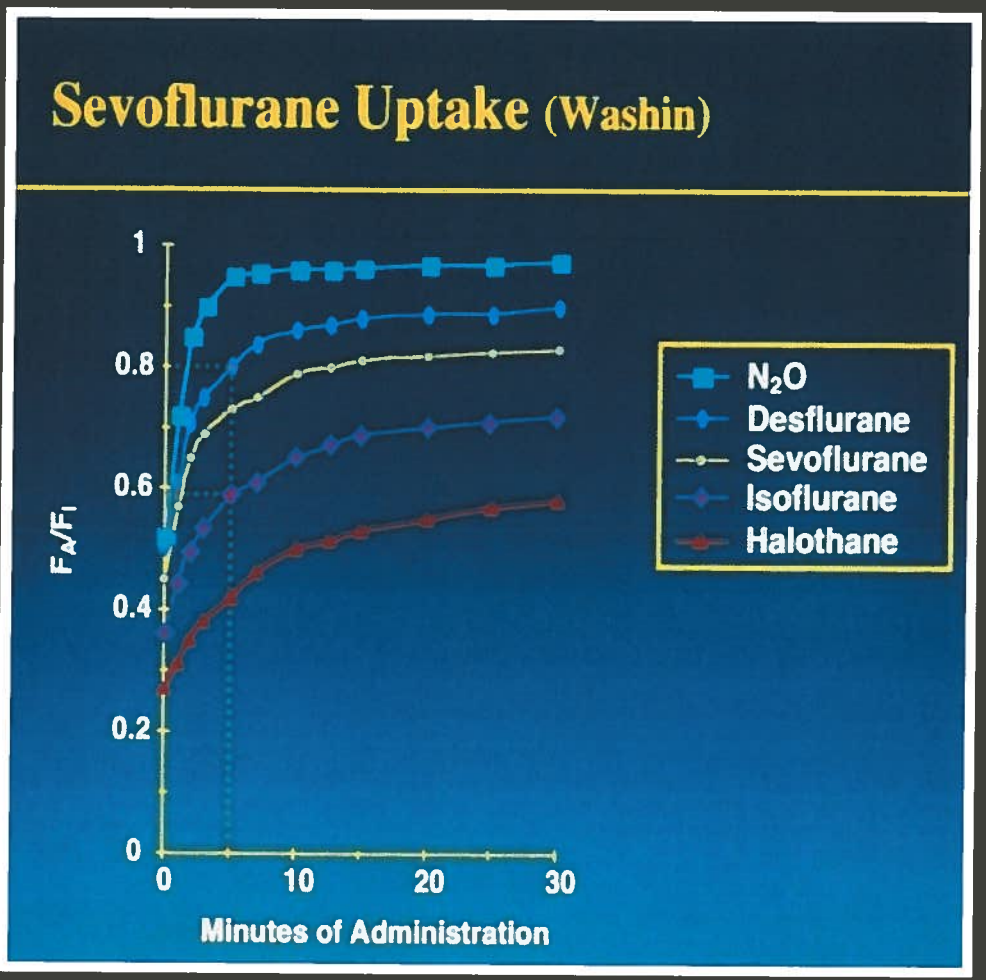
Uptake and Distribution

- administered via respiratory route
- onset and offset determined by
  - blood:gas solubility coefficient
- other factors that determine onset
  - minute ventilation
  - inspired concentration
  - cardiac output
- effect of congenital heart disease
  - left-to-right shunt
  - right-to-left shunt

Blood:Gas Partition Coefficients of Anesthetic Agents



Sevoflurane Uptake (Washin)



Yasuda N et al, *Anesth Analg* 1991;72:316

Partition Coefficients of Anesthetic Agents

	Blood:Gas	Brain:Blood	Fat:Blood	Oil:Gas
Halothane	2.5	1.9	51	224
Enflurane	1.8	1.3	42	96.5
Isoflurane	1.43	1.6	45	90.8
Methoxyflurane	15	1.4	38	970
Sevoflurane	0.65	1.7	47	47.2
Desflurane	0.45	1.3	27	18.7
N_2O	0.47	1.1	2.3	1.4

Inhalational Anesthesia

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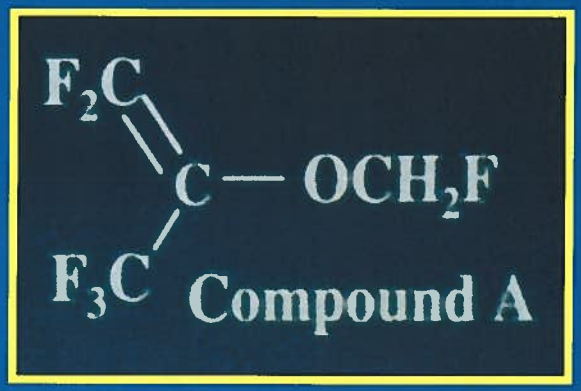
Inhalational Anesthetic Agents: Metabolism

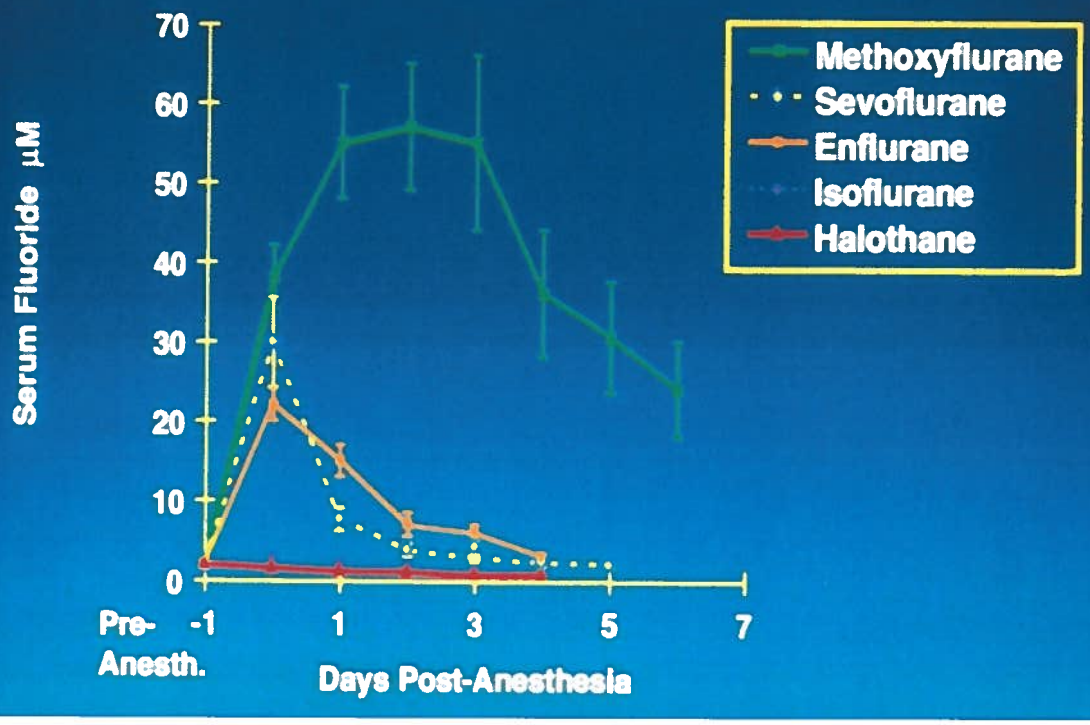
Methoxyflurane	50%
Halothane	20%
Enflurane	3-4%
Isoflurane	0.2%
Sevoflurane	3-5%
Desflurane	0.02%

Sevoflurane Metabolism

- fluoride
- compound A
  - fluorinated vinyl
- HFIP not TFA



Comparison of Inorganic Fluoride



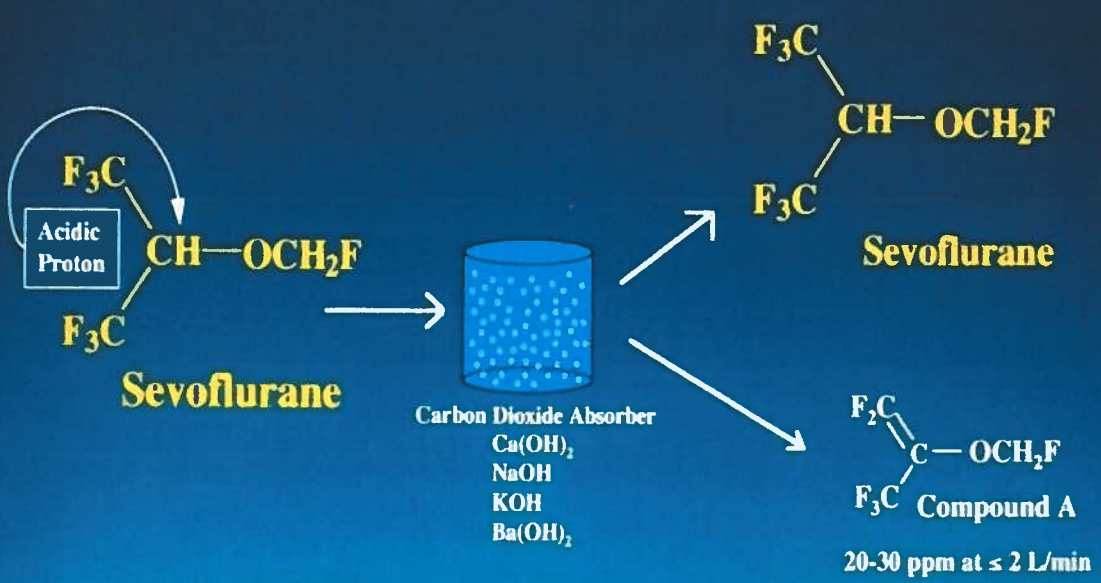
Methoxyflurane Metabolism

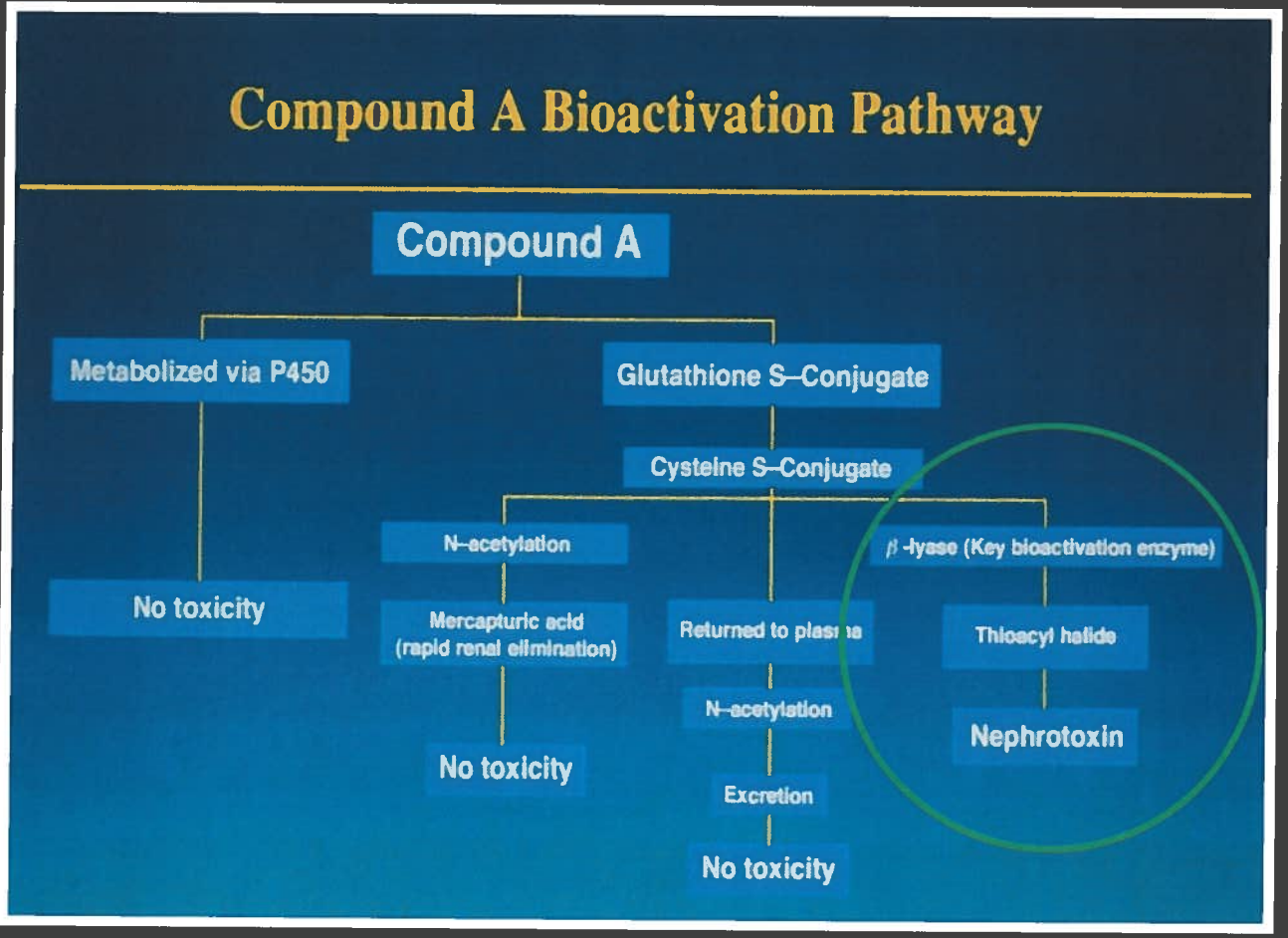
- cytochrome P_{450}
- present in both liver and kidneys
- local fluoride production in kidneys
  - fluoride concentration in kidney > blood
- nephrotoxicity at 50 μmol/liter in blood

Sevoflurane Metabolism

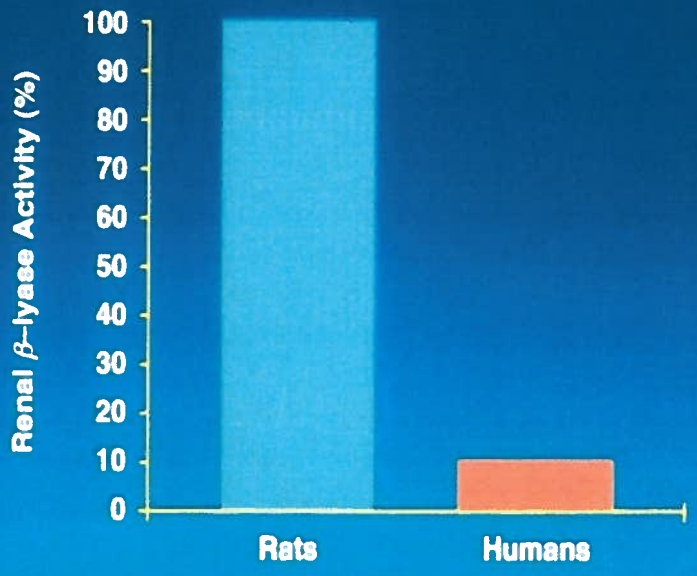
- cytochrome P_{450} 2E1
- present only in liver
- fluoride concentration in blood > kidney
- no significant risk of toxicity

Formation of Compound A




Compound A Bioactivation Pathway
Compound A
Metabolized via P450
Glutathione S–Conjugate
No toxicity
Cysteine S–Conjugate
N–acetylation
β -lyase (Key bioactivation enzyme)
Mercapturic acid
(rapid renal elimination)
Returned to plasma
Thioacyl halide
N–acetylation
Nephrotoxin
No toxicity
Excretion
No toxicity

Renal β-lyase Activity in Humans Versus Rats for Compound A



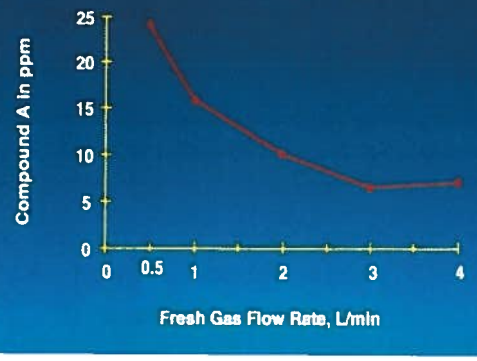
Lash LH et al, *Drug Metab Dispos* 1990;18:50

Compound A Production

- sevoflurane concentration
- type of CO_2 absorbent
- fresh gas flow rate
- temperature (CO_2 production)
- time
- water content

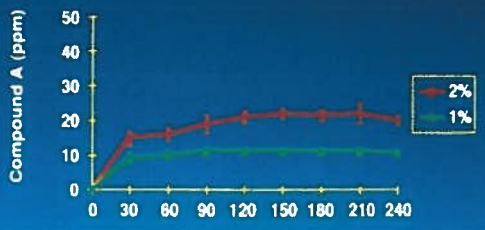
Compound A Production

Flow Rate of Anesthetic Gases



Sevoflurane Concentration

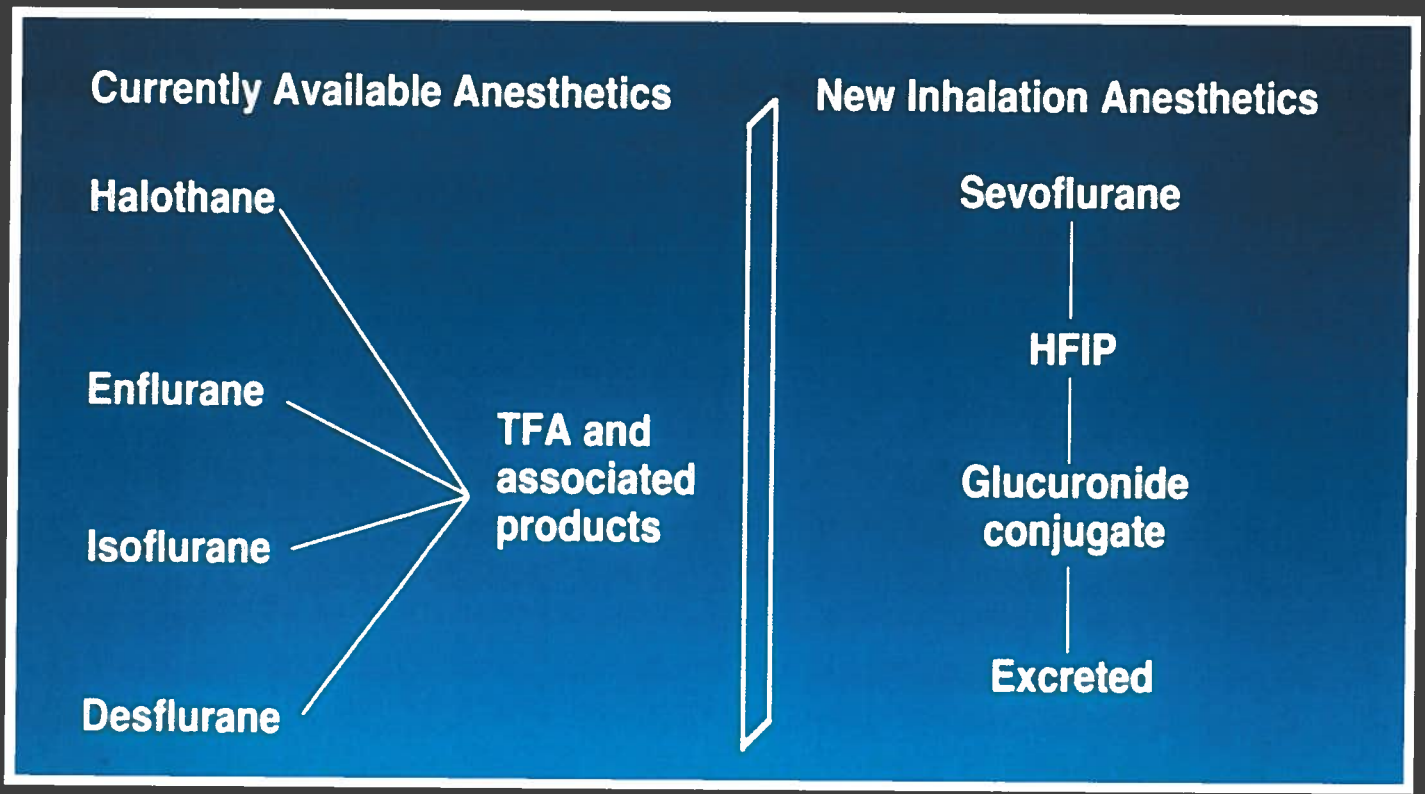
Compound A levels at two sevoflurane concentrations (1 and 2%) in a model circuit (laboratory studies) with soda lime as the CO_2 absorbent.



Inhalational Anesthesia

- metabolism →
  - HFIP (hexafluoroisopropanol)
  - TFA (trifluoroacetic acid)
- HFIP is glucuronidated and renally eliminated
- HFIP is less reactive than TFA
  - TFA can act as a hapten → hepatoxicity
- no evidence of hepatotoxicity of HFIP

Hepatotoxicity



CO_2 Absorber: Agent Degradation

- compound A
  - sevoflurane
- carbon monoxide
  - desflurane
  - isoflurane
  - enflurane
- anesthetic agent destruction
  - increased cost

Desflurane & Carbon Monoxide

- CO_2 absorbent
  - dessicated
  - Baralyme > soda lime
  - flow $\geq$ 3 liters/minute
- scenario
  - Monday AM case
  - rare reports of toxicity

Carbon Monoxide Production in Dry Soda Lime at 35°C

	PPM-min	
Absorbent	Desflurane	Isoflurane
Soda lime, dry	1800	349
Soda lime, 1.4% water	26	23
Baralyme, dry	11,600	851
Baralyme, 1.6% water	5910	725

Fang et al. Anesth Analg. 1995;80:1187

CO_2 Absorber: Agent Degradation

- sodalime - barium hydroxide lime (Baralyme®)
  - sodium and potassium hydroxides
- abstract labile proton from anesthetic agents
  - more susceptible to degradation
- new carbon dioxide absorbers
  - decreased amounts of strong bases
    - Dragersorb 800 Plus®, Medisorb®, Spherasorb®
      - no potassium hydroxide
      - do contain sodium hydroxide and calcium hydroxide
  - elimination of strong bases
    - Amsorb® (calcium hydroxide)

Sevoflurane: Will My Patient Ignite?

ARDS from exothermic Baralyme-sevoflurane reaction.

Fatherce RS, Leighton BL, *Anesthesiology* 2004;101:531

Spontaneous ignition, explosion and fire.

Wu J et al, *Anesthesiology* 2004;101:534

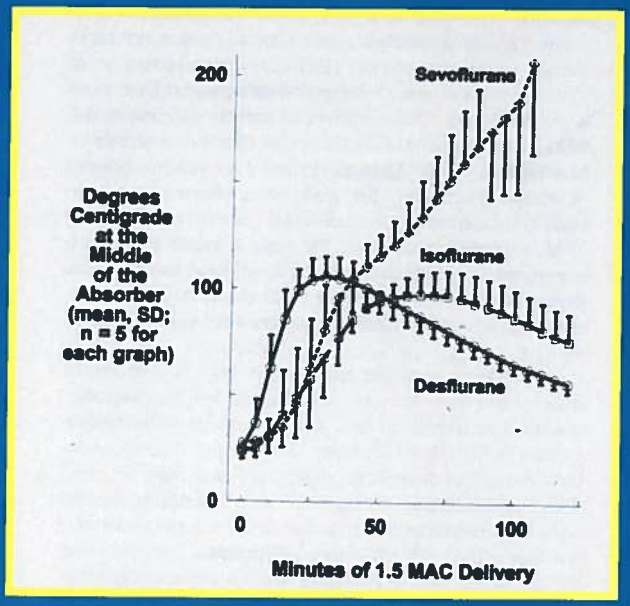
Explosion with Baralyme, sevoflurane, and high gas flows.

Castro BA et al, *Anesthesiology* 2004;101:537

Sevoflurane and Desiccated Absorbent

Laster M et al. *Anesth Analg* 2004;99:769

- *in vitro* experiment
- Baralyme dessicated®
  - 3.5 kg of Baralyme® in a 4 liter flask
  - 10 lpm oxygen flow + flask warmed
  - flow continued until weight of flask no longer changed (2-3 days)
- 1.5 MAC inhalational agent
  - F_iO_2 1.0 at 6 lpm



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Cardiovascular Effects

- dose dependent effects
- modified by
  - co-morbid diseases
  - intravascular volume status
- halothane
  - primary cause of intraoperative cardiac arrest
- varying effects on SVR, HR, and contractility

Cardiovascular Effects

- sevoflurane
  - decreased HR and cardiac output
- isoflurane and desflurane
  - vasodilatation and sympathetic stimulation
    - increased heart rate
    - potential for coronary steal
  - decreased afterload → increased cardiac output

Sevoflurane, Bradycardia & Trisomy 21

Roodman S et al, *Paediatr Anaesth* 2003;13:538

- case series of 3 patients with trisomy 21
- 2 without CHD, normal echocardiogram and ECG
- one required IV epinephrine

Wickham Kraemer et al, Anesth Analg 2010;111:1259

- retrospective review: 208 with trisomy 21 vs. 268 control patients
- higher incidence of bradycardia and hypotension: 57% vs. 12%
- greater use of anitcholinergic agents: 24% v 0%, $p<0.001$

Desflurane & The Sympathetic NS

- transient response, treatment generally not needed
- does not occur in all patients, less likely in elderly
- opioids or α_2-adrenergic agonist control response
- more common with
  - rapid increase in inhaled concentration
  - increase from 1.0 to 1.5 MAC than from 0.5 to 1.0 MAC
- avoid by slow increments in vaporizer setting
  - start at 3-6%
  - start at 6-8% with low flows (0.5-1 liter/minute)
- if treatment necessary
  - short acting β-adrenergic antagonist

Myocardial Preconditioning

Li F et al, *Acta Anesthesiologica Sinica* 2000;38:113

- Langendorff model, laboratory animal (rats)
  - 15 min perfusion, 20 min ischemia, 60 min reperfusion
- four groups
  - control (no pretreatment)
  - isoflurane 1.4%
  - sevoflurane 1.7%
  - two 5-minute ischemic periods separated by 5 min perfusion
- sevoflurane, isoflurane, and ischemic group vs. control
  - recovered left ventricular contractility better
  - less ischemic damage by histological examination

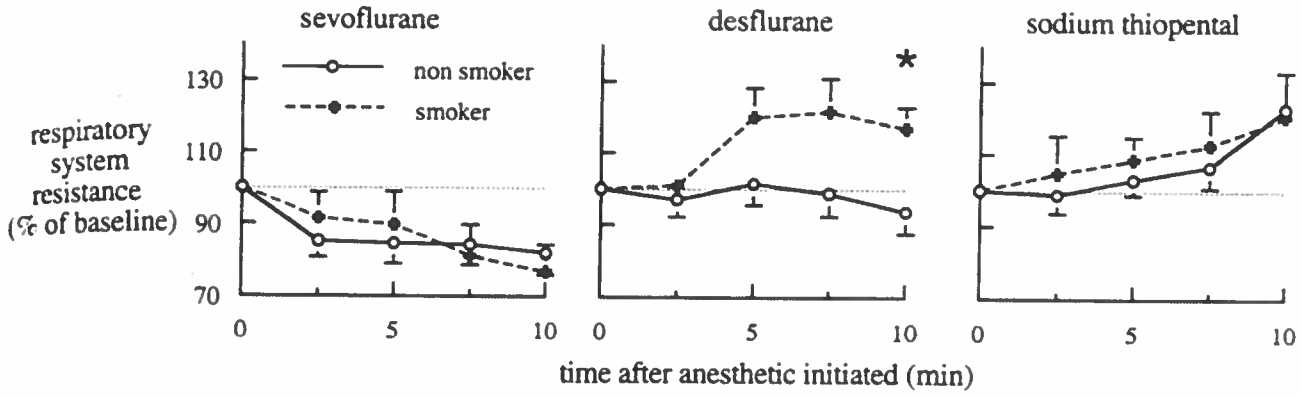
Respiratory Effects

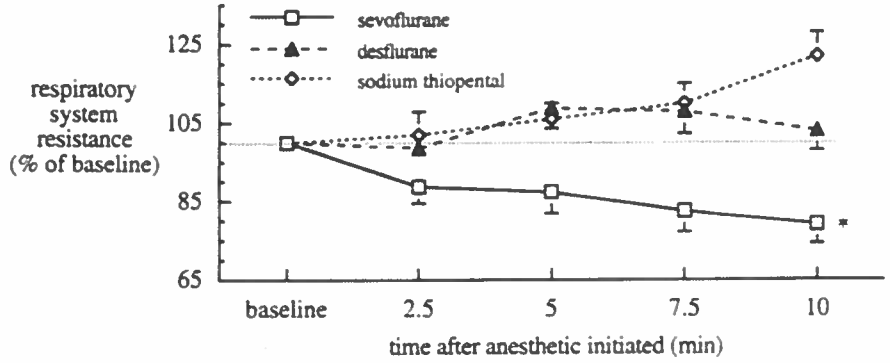
- dose dependent, modified by co-morbid diseases
- decreased alveolar ventilation
  - primarily tidal volume → hypercarbia
- inhibit CNS response to hypoxia + hypercarbia
- inhibit hypoxic pulmonary vasocontriction
  - worsening oxygenation
- bronchodilatation
  - direct effect on smooth muscle

Sevoflurane & Desflurane: Airway Reactivity

Goff MJ et al, *Anesthesiology* 2000;93:404

- prospective trial in 50 adults
- thiopental induction, endotracheal intubation
- maintenance anesthesia
  - thiopental infusion (0.25 mg/kg/hr)
  - desflurane 1 MAC
  - sevoflurane 1 MAC
- determination of respiratory resistance


sevoflurane
desflurane
sodium thiopental
non smoker
smoker
respiratory system resistance (% of baseline)
130
110
90
70
0
5
10
*
time after anesthetic initiated (min)


sevoflurane
desflurane
sodium thiopental
respiratory system resistance (% of baseline)
125
105
85
65
baseline
2.5
5
7.5
10
*
time after anesthetic initiated (min)

CNS Effects

- sedation, amnesia, general anesthesia
- decreased $CMRO_2$
- slowing of the EEG → isoelectric
- occasional CNS stimulation
  - sevoflurane, enflurane
- increased CBF and increased ICP
  - least with isoflurane
  - blunted by hypocarbia

Sevoflurane: CNS Effects

Kaike KK et al, *Anesthesiology* 1999;91:1952

- case report, 2 adult patients, study on CBF
- paroxysmal EEG potentials during sevoflurane at 4%

Yli-Hankala A et al, *Anesthesiology* 1999;91:1596

- 30 woman, spontaneous or controlled hyperventilation
- epileptiform EEG activity (spikes or polyspikes)
  - 15/15 with controlled hyperventilation (3 also had clonic movements)
  - 7/15 with spontaneous ventilation

Inhalational Anesthesia

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- ***clinical applications***
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Clinical Applications

- ***procedural sedation***
- ICU sedation during mechanical ventilation
- status asthmaticus
- status epilepticus

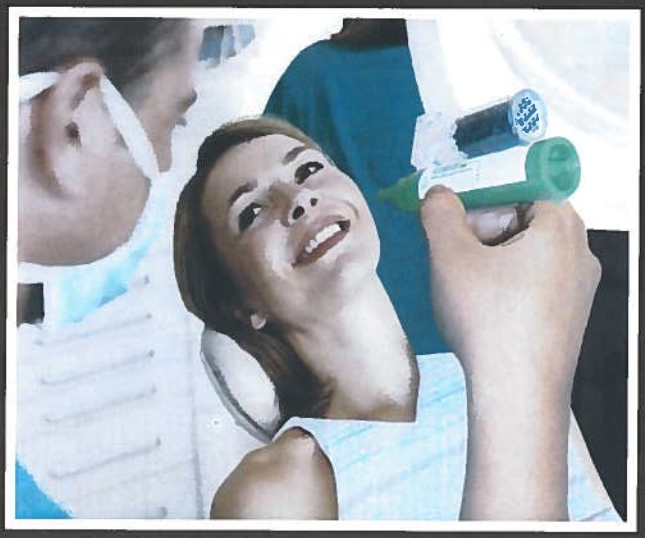
Procedural Sedation: Sevoflurane

Sury MRJ et al, *Pediatr Anesth* 2007;17:148

- prospective, observational case series
- 13 infants, 7 former preterm
  - median post-conceptional age: 46 wks (40-70)
  - median weight: 4.4 kg (3.3-6.5 kg)
- nasal insufflation of sevoflurane
  - nasal cannulae, oxygen flow at 2 liters/minute
  - sevoflurane vaporizer set at 4% (range: 4-8%)
- successful in 12 (6 asleep within 10 minutes)
- rapid recovery
- one episode of desaturation, airway repositioned

Procedural Sedation: Methoxyflurane

- licensed for use in
  - Australia, New Zealand, Middle East
- issues with renal toxicity (flouride)
- Penthrox Inhaler™
  - Medical Developments International (Victoria, Australia)
  - tubular hand held device, 22 mm mouthpiece
    - can also use standard anesthesia mask
    - oxygen inlet to administer supplemental oxygen
  - primed with liquid methoxyflurane
  - one-way valve, exhalation through separate chamber
    - charcoal
  - dilutor hole (can vary concentration from 0.1-0.4%
  - used on US reality TV show Survivor



Procedural Sedation: Methoxyflurane

Babl F et al, *Pediatr Anesth* 2007;17:148

- prospective, observational case series
- 14 children, 6-13 years of age, extremity injuries
- used both for analgesia and procedural sedation
  - 4 to 25 minutes
  - intermittently (7) and continuously (7)
- no adverse effects
- efficacy
  - 4 with fractures and high pain scores: satisfactory analgesia
  - 4 with fractures and low pain scores: minimal effect
  - 6 for procedural sedation: effective
  - 13 of 14 would chose methoxyflurane again

Clinical Applications

- procedural sedation
- ***ICU sedation during mechanical ventilation***
- status asthmaticus
- status epilepticus

Inhalational Anesthetic Agents: Advantages

- large clinical experience in Europe
- easy to titrate
- inhalational administration
- rapid onset and offset
- amnesia, sedation, and analgesia
- limited development of tolerance
- beneficial physiologic effects
  - anti-convulsant
  - bronchodilator
  - cerebral protection
  - myocardial preconditioning

Inhalational Anesthesia: PICU Sedation

Arnold JH et al, *Anesth Analg* 1993;76:520

- prospective study, isoflurane in 10 pediatric patients
  - 3 weeks to 10 years of age
  - inspired concentration adjusted by ICU physician
  - opioids and benzodiazepines tapered
- duration of sedation
  - 29 to 769 hours (mean: 245 hrs)
  - 13 to 497 MAC-hours (mean: 131)
- findings
  - highest fluoride concentration: 26.1 μmol/L
  - decreased creatinine clearance: 1 of 5
  - increased LFT's: 3 of 10
  - abstinence syndrome: 5/10 (all received ≥ 70 MAC-hours)

AnaConDa™ vs. Midazolam

Sackey P et al, *Crit Care Med* 2004;32:2241

- prospective trial, 40 adult ps, mechanical ventilation
- isoflurane (AnaConda™) versus midazolam

Medication	*Isoflurane*	*Midazolam*
Time within desired range of sedation	59%	54%
Time to extubation (minutes)	10 ± 8	252 ± 271
Time to follow commands (minutes)	10 ± 8	110 ± 132

Inhalational Anesthesia in the PICU

- retrospective evaluation of sedation - 29 pediatric patients
  - upper airway issues: croup or epiglottis
  - 12 of 29 received isoflurane (inspired concentration of 0.25-1.5%)
- withdrawal phenonmena
  - ataxia, agitation, hallucinations and confusion
  - not if administered for ≤ 15 hours

Kelsall AWR et al, *Crit Care Med* 191994;22:1032

- CDH repair while on ECMO in 13 neonates
- fentanyl 22 µg/kg/hr + bolses (n=7) vs. isoflurane (n=6)
- fentanyl patients
  - higher MAP and HR during procedure
  - 7/7 received SNP vs. 1/6 with isoflurane

Atkinson JD et al, *ASAIO* 1994;40:986

Inhalational Anesthesia Withdrawal

- 4-year-old, 19 days of isoflurane (ET = 0.8-1.2%)
  - follows commands
  - MAC-awake = 0.3-0.4 MAC (isoflurane = 0.4-0.5%)
- 32 days of administration, agent stopped
  - agitation, diaphoresis, tachycardia, hypertension, diarrhea

Arnold JH et al, *Anesthesiology* 1993;78:985

- 7-year-old boy
- isoflurane, unspecified concentration for 4 days
- agitation, visual and auditory hallucinations, seizure

Hughes et al, Acta Paediatr 1993;82:885

Clinical Applications

- procedural sedation
- ICU sedation during mechanical ventilation
- ***status asthmaticus***
- status epilepticus

Inhalational Anesthesia: Asthma

- first reports appeared in 1930's
  - ether, cyclopropane
- modern day anesthetics (halothane) in 1970's
- remains primarily anecdotal
- airway effects of inhalational anesthetic agents
  - blunts reflex bronchoconstriction
  - direct effect on intracellular calcium
    - smooth muscle relaxation

Inhalational Anesthesia: Asthma

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

- case series of 6 pediatric patients
- appendix outlining their protocol

Table 1. Summary of isoflurane experience with six pediatric patients

Preisoflurane Patient	Age/Sex	pH	$Paco_2$ (torr)	PIP (cm H_2O)
1	13 yrs/F	7.27	77	62
2	14 yrs/M	6.96	96	60
3	10 yrs/M	6.99	110	60
4	15 yrs/M	7.05	85	64
5	15 months/F	7.07	72	>30 (anesthesia bag)
6	14 months/F	Unavailable	>60[a]	60–65

Postisoflurane Patient	Elapsed Time	pH	$Paco_2$ (torr)	PIP (cm H_2O)
1	10 mins	7.45	45	45
2	30 mins	7.30	44	45
3	30 mins	7.30	50	35
4	40 mins	7.08	65	45
5	78 mins	7.18	59	22
6	12 mins	7.28	48	35

PIP, peak inspiratory pressure; To convert torr to kPa, multiply value by 0.1333.
[a]End-tidal CO_2 monitoring.

Isoflurane & Asthma: Entry Criteria

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

- intubated patient with status asthmaticus
- peak inspiratory pressures of $\geq$ 40 cmH_2O
- maximal medical therapy
  - intravenous corticosteroids
  - magnesium
  - anticholinergic therapy
  - terbutaline $\geq$ 5.0 µg/kg/min

Isoflurane & Asthma: Protocol

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

- isoflurane
  - start therapy at 1-2%, adjust by 0.1% every 5–10 minutes
  - goal: PIP $\leq$ 35 cm H_2O
  - maintain for 2–4 hours before weaning the medication
- discontinue sedation and neuromuscular blocking agents
  - isoflurane $\geq$ 1%
- continue intravenous β-adrenergic agonists
  - unless the patient develops ventricular arrhythmias
  - differing mechanisms of action
- continue inhaled anticholinergic agents and β-adrenergic agonists
- maintain serum magnesium levels of 3.0–4.0 mg/dL
- continue intravenous corticosteroid therapy

Isoflurane & Asthma: Complications

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

- hypotension
  - volume replacement with crystalloid up to 40-60 mL/kg
  - vasopressor therapy
    - epinephrine at 0.05 μg/kg/min or dopamine at 5 μg/kg/min
- arrhythmias
  - maintain normal potassium, magnesium, and calcium
  - discontinue β-adrenergic therapy
  - discontinue isoflurane
- nephrotoxicity or hepatotoxicity
  - follow serum electrolytes, BUN, creatinine, hepatic enzymes
  - urine output
  - serum fluoride
    - decrease or discontinue isoflurane if $\geq$ 30 μM.

Isoflurane & Asthma: Weaning

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

- PIP ≤ cm H_2O with tidal volumes ≥ 8 mL/kg
  - $PaCO_2$ <60 mmHg and pH ≥ 7.2
  - decrease isoflurane by 0.1% every 20–30 minutes
- isoflurane ≤ 1%
  - reinstitute sedation and analgesia as needed
  - reinstitute β-adrenergic agonist therapy

Clinical Applications

- procedural sedation
- ICU sedation during mechanical ventilation
- status asthmaticus
- ***status epilepticus***

Inhalational Anesthesia: Status Epilepticus

- dose-dependent effects
  - slowing and decreased amplitude of EEG signals
  - burst suppression – isoelectric EEG
- reports are anecdotal
  - first pediatric case reported in 1985
- recent concern regarding potential neurotocity

  Fugate JE et al, *Anesth Analg* 2010;111:1520
- use included in published SE protocols

  Delgado-Escueta AV et al, *New Engl J Med* 1982;306:1337

  Haafiz A et al, *Pediatr Emerg Care* 1999;15:119

Isoflurane & Status Epilepticus

Kofke WA et al, *Anesthesiology* 1989;71:653

- largest case series of pediatric patients
  - 11 applications in 9 patients, 6 were 2-13 years of age
- failure of conventional therapy
  - phenobarbital, benzodiazepines, phenytoin
- isoflurane effective
  - seizures recurred in 8 of 11 when isoflurane decreased
  - 6 of 9 patients died, cognitive deficits in remaining 3
- adverse effects
  - hypotension, n=1
  - elevated serum fluouride concentration, n=1

Inhalational Anesthesia

- history
- chemical structure & physical properties
- metabolism & interactions
- end-organ effects & adverse effects
- clinical applications
- ***delivery in the ICU***

Inhalational Agents: Disadvantages

- equipment
  - delivery, monitoring, scavenging
- cost of agent and equipment
- who adjusts concentration
- physiologic effects
  - hepatitis
  - cardiovascular depression
  - cerebral vasodilatation
  - fluoride release (renal effects)
  - MH triggering agent
- altered metabolism of other drugs

Isoflurane in the PICU: Monitoring & Equipment

Wheeler DS et al, *Pediat Crit Care Med* 2000;1:59

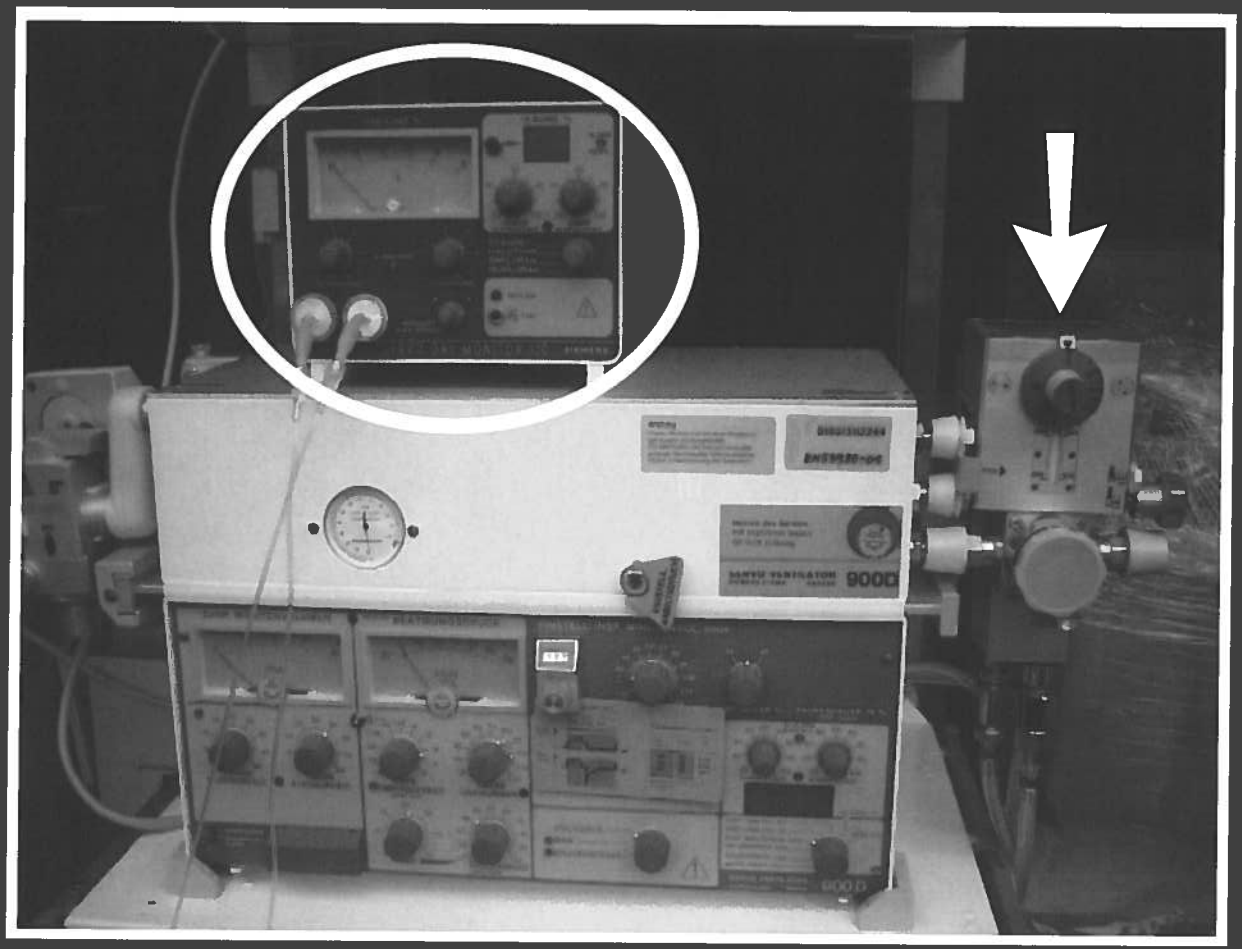
- machine for delivery
- anesthesia gas scavenging system
- end-tidal CO_2
- cardiorespiratory support with pulse oximetry
- arterial access for BP and ABG monitoring
- central venous access
- in-line volatile gas analyzer for anesthetic agent
- closed system for suctioning

OHSA requirements
Suctioning issues – patient disconnects

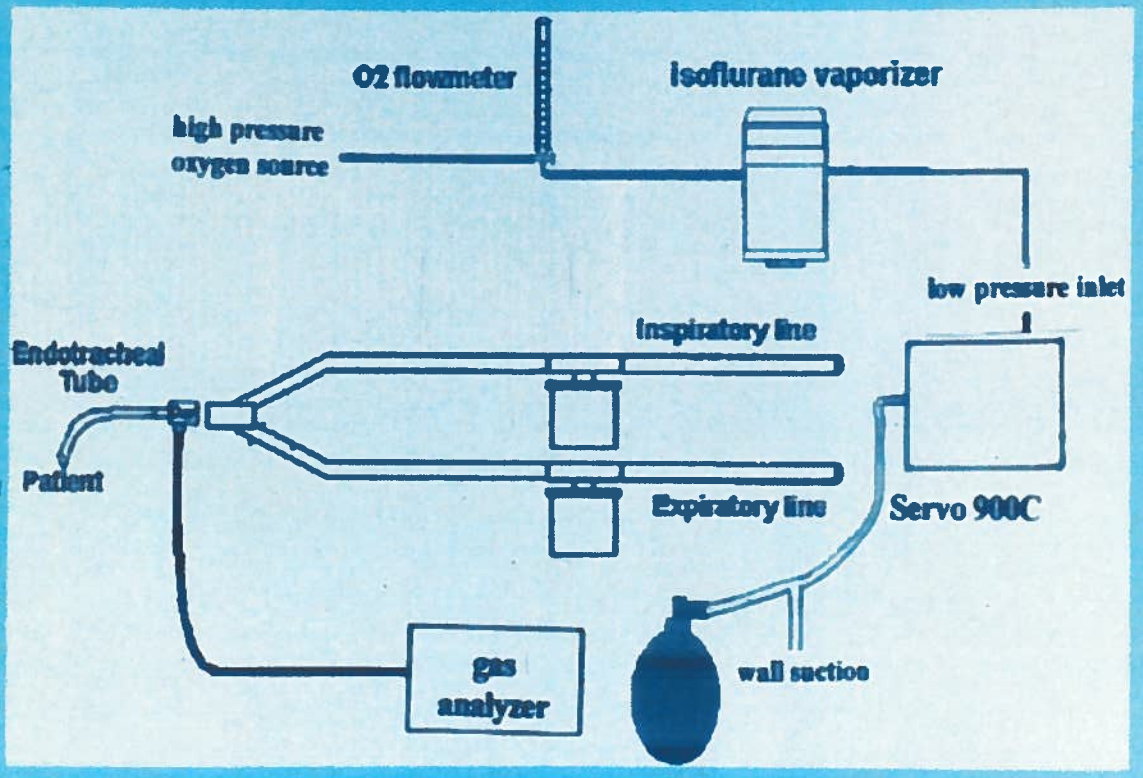
Inhalational Agents: PICU Delivery

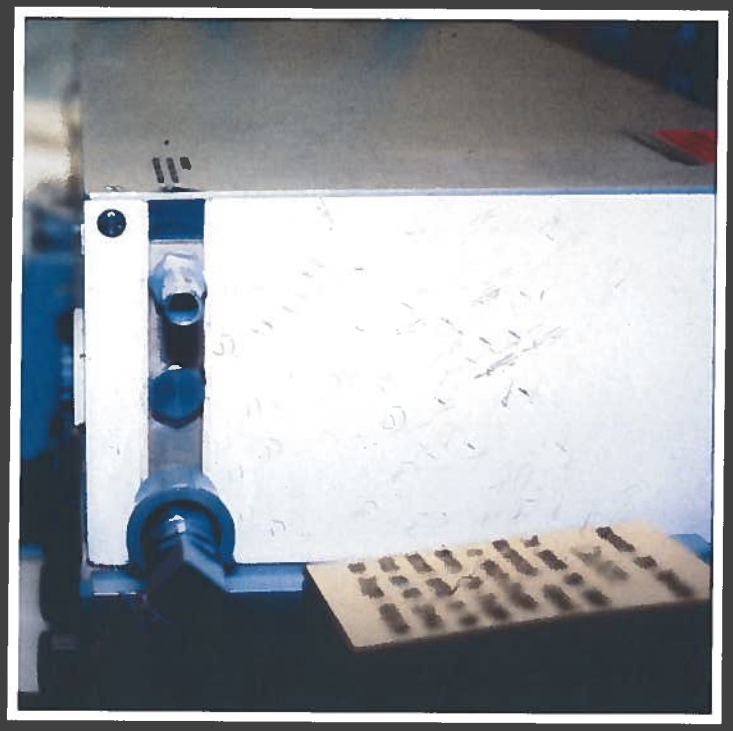
- move patient to operating room
- use anesthesia machine in Pediatric ICU
  - quick and easy, limited preparation time
  - ICU ventilators are not meant for sick patients
    - limited modes of ventilation, PEEP, PIP
- middle ground
  - Serve 900D anesthesia machine
- modify ICU ventilator
- administer it using ICU ventilator
  - vaporizer in-line of inspiratory limb
  - into inspiratory limb
  - Servo 900 C

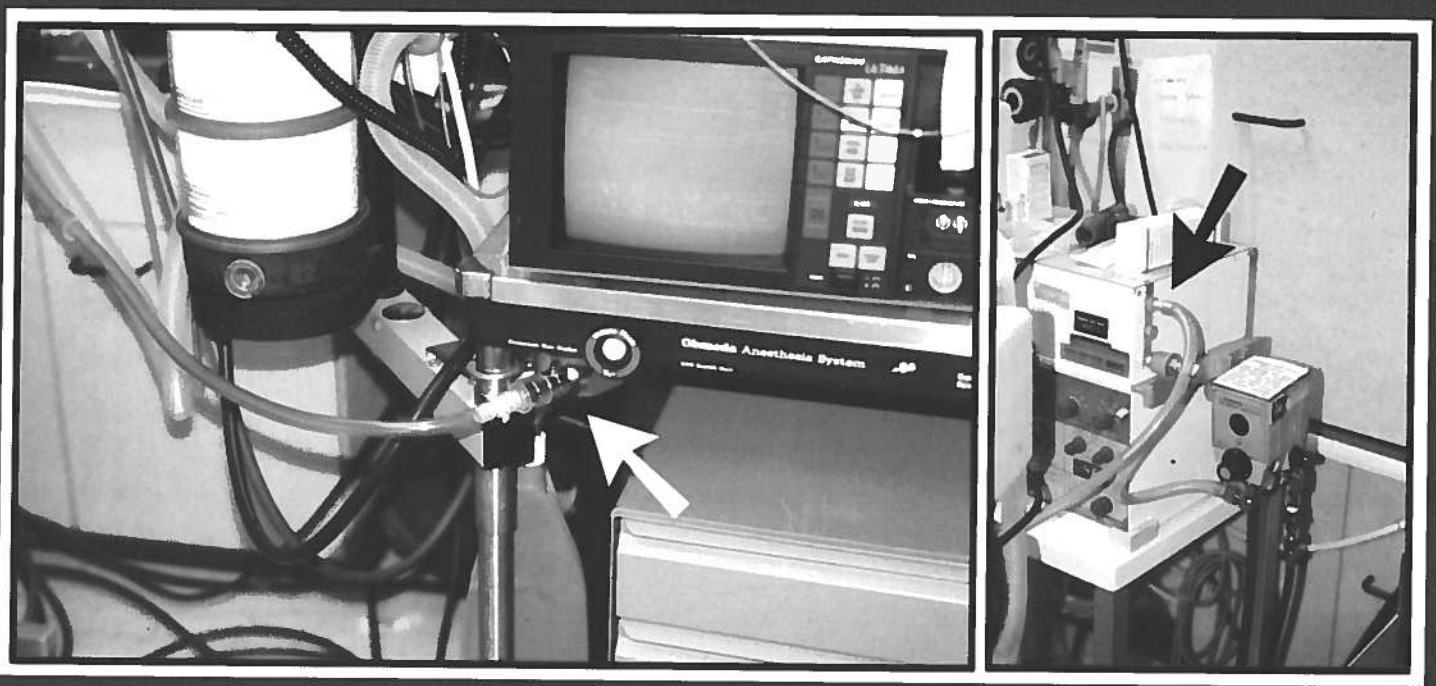
Servo 900D Anesthesia Machine



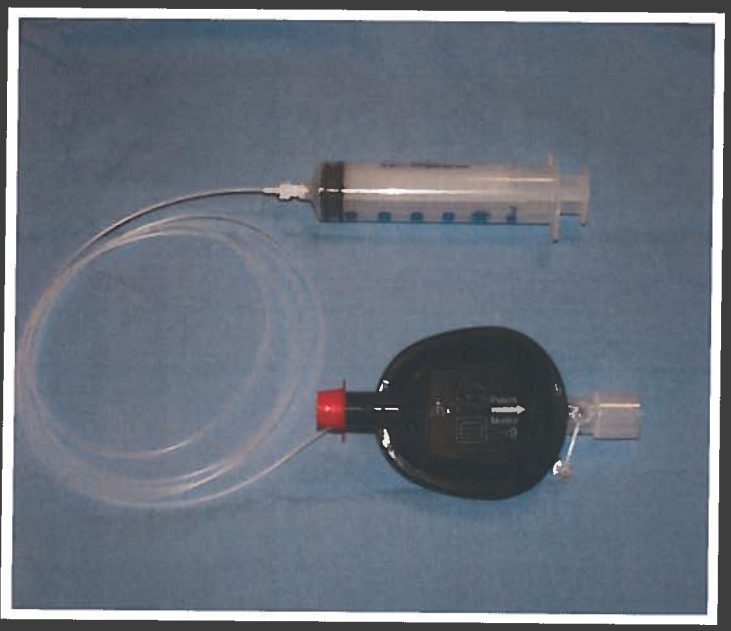
Isoflurane through the Servo 900C

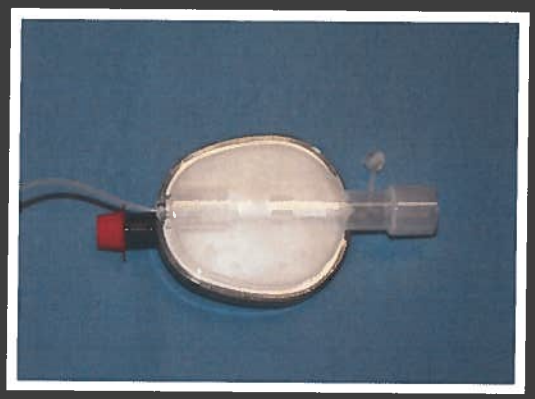


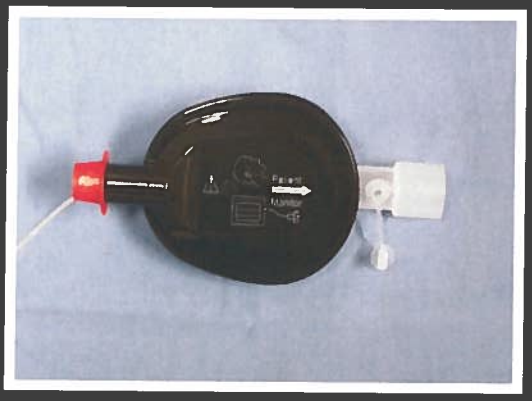


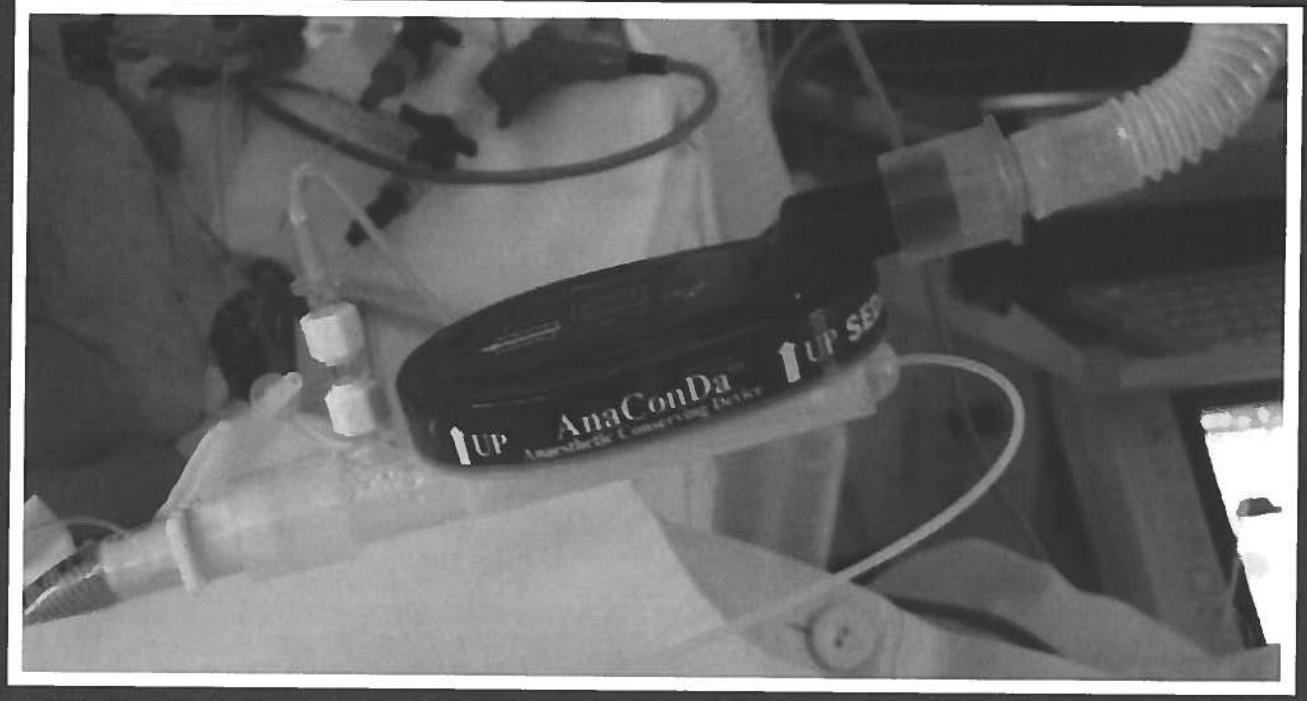

Ohmeda Anesthesia System

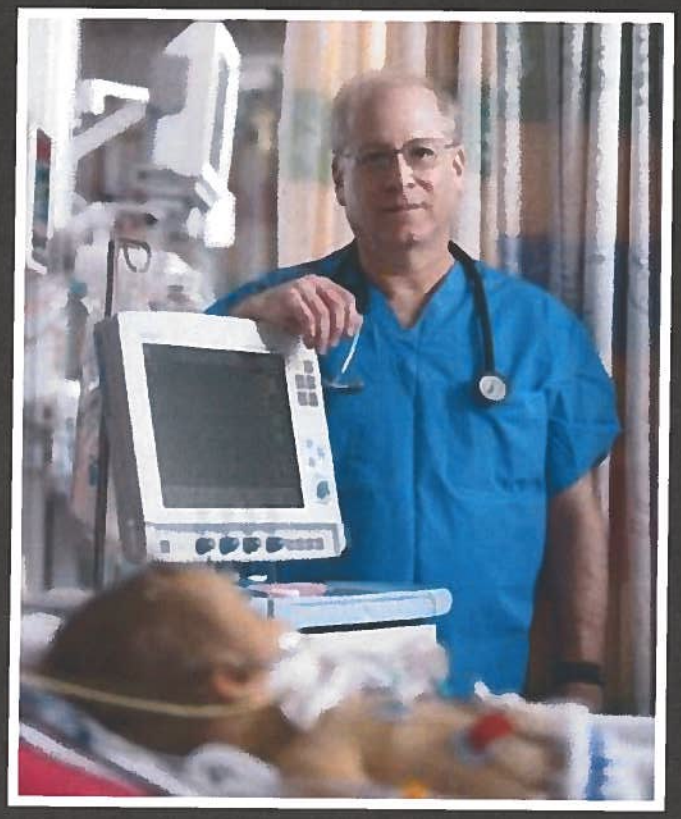
AnaConDa™ = Anesthesia Conserving Device, Hudson RCI, Uplands Vasby, Sweden

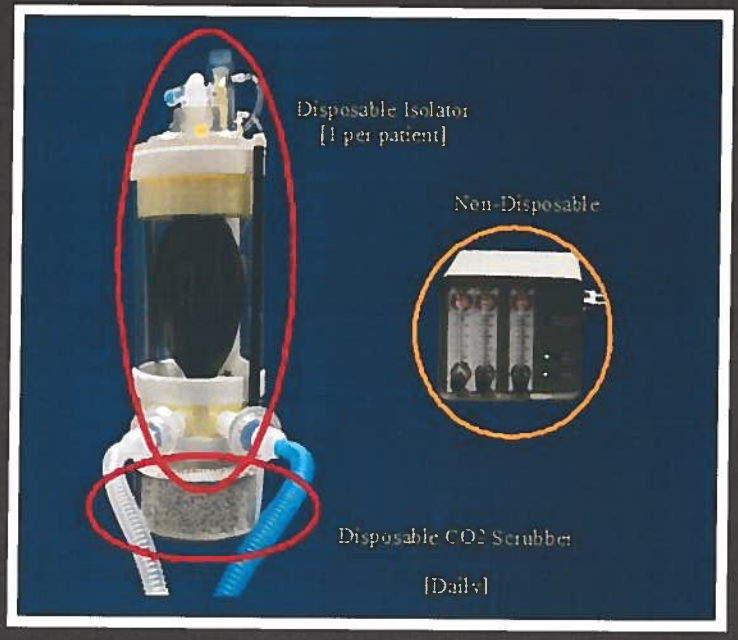







UP
AnaConDa




Disposable Isolator
[1 per patient]
Non-Disposable
Disposable CO2 Scrubber
[Daily]

Maquet Flow –I Anesthesia Ventilator

Inhalational Anesthesia

- history
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Therapeutic applications and uses of inhalational anesthesia in the pediatric intensive care unit.

Joseph D. Tobias, MD

Pediatr Crit Care Med 2008;9:169-179.