Volatile Sedation for Critical Care Patients

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Disclosures

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Volatiles…beyond the operating room

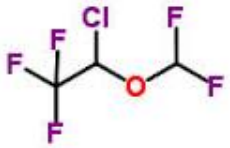
Lecture Objectives

- What are volatile anesthesia agents?
- Why volatile ICU sedation?
- Sedation studies
- ICU delivery of volatiles agents

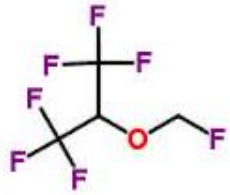
What are Volatile Anesthetic Agents?

19th Oct 1846 RC Hinckley: "The First Operation Under Ether"
Massachusetts General Hospital

Dr. William Morton (dentist) provides ether anesthesia to patient Gilbert Abbott.
Dr. John Warren (surgeon) excised a vascular neck tumor.



Isoflurane



Sevoflurane

Desflurane

Volatile Anesthetic Agents

- Family of hydrocarbon flourinated ethers
- Liquid at room temperature which require vaporization for administration

Dose

1 MAC
Surgical
Anesthesia

0.3 MAC
Sedation

Hypnosis, anti-convulsant, amnesia

Hypotension, Cardiac depression

Respiratory Depression

Shivering
Nausea
Vomiting

Miscellaneous

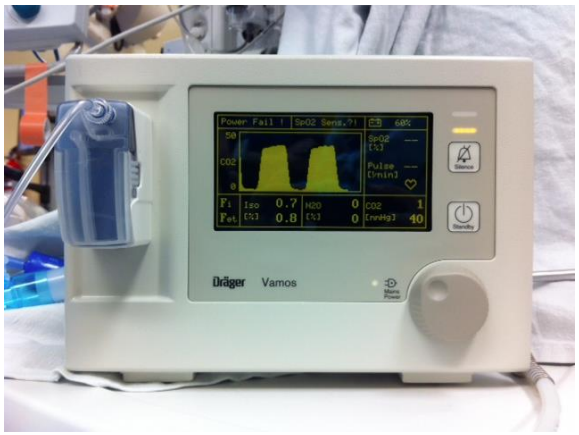
Traditional uses of volatiles in ICU

- Refractory status asthmaticus
- Refractory status epilepticus
- Complex sedation scenarios

Bierman MI et al. Crit Care Med 1986; 14: 832; Soukup J Crit Care 2009; 24: 535

Why Volatile Sedation?

- Titratable clinical effect
- Low doses (0.1-0.3 % Isoflurane, 0.3-0.5% sevoflurane)
- Cardiovascular stability
- Rapid onset/offset
- Low systemic metabolism (isoflurane 0.2%,sevoflurane 3%,desflurane 0.002%)
- End-tidal gas measurement
- Low Cost
- ? end organ protection



Sedation Studies

Isoflurane compared with midazolam for sedation in the intensive care unit.

Kong KL, Willatts SM, Prys-Roberts C. *BMJ 1989; 298: 1277-80*

	Group given isoflurane	Group given midazolam
Stopping sedation to tracheal extubation:		
No of patients	14	13
Median (range) (min)	60 (30-135)	195 (50-1080)
Approximate 95% confidence interval for difference in median	45 to 205	
p Value	0·0016	
Stopping sedation to writing home address:		
No of patients	16	12
Median (range) (min)	58 (20-270)	275 (75-1440)
Approximate 95% confidence interval for difference in median	105 to 390	
p Value	0·0001	
Stopping sedation to moving toes to command:		
No of patients	29	27
Median (range) (min)	0 (0-10)	0 (0-300)
Approximate 95% confidence interval for difference in median	−0·1 to 10·1	
p Value	0·0167	
Stopping trial sedative to need for resedation:		
No of patients	12	14
Median (range) (min)	15 (5-230)	108 (5-490)
Approximate 95% confidence interval for difference in median	45 to 120	
p Value	0·0014	

- RCT, 60 adult ICU patients
- Midazolam vs. Iso for < 24 hr

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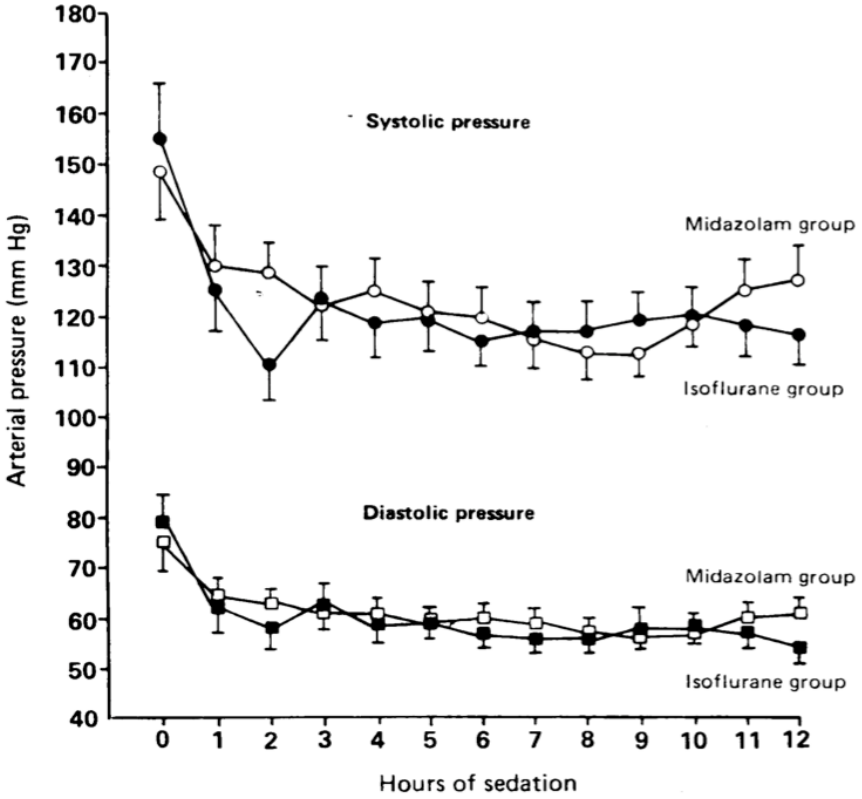
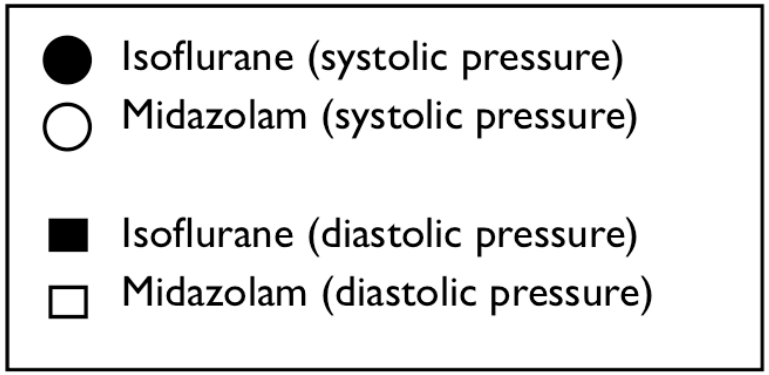


FIG. 1—*Changes in arterial pressure for first 12 hours after patients were sedated. Values are means (SE) of systolic pressure for patients given isoflurane (●) or midazolam (○) and diastolic pressure for patients given isoflurane (■) or midazolam (□)*



Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery.

Hellstrom J, Owall A, Sackey PV. *Scand Cardiovasc J 2012; 46: 262*

- n=100, post ACB patients
- Sevoflurane vs. Propofol for 2-3 h
- Median time to extubation
  10 (10-100) vs. 25 (21-240) mins, $p < 0.001$
- No difference pain/agitation/shivering/nausea and vomiting/length of ICU stay

Volatile-based short-term sedation in cardiac surgical patients: A prospective randomized controlled trial.

Jerath A, Beattie S, Wasowicz M et al. *Crit Care Med 2015;43:1062*

- RCT 150 adult post-ACB 2009-2011
- Grade 1/2 LV function
- Isoflurane/sevoflurane volatile anesthesia (0.6-2MAC) + sedation (0.3 MAC) vs. i.v propofol 2mg/kg/h
- Primary outcomes: Troponin leak
- Secondary outcomes: Extubation times, pain scores, shivering, PONV

	Volatile (N=67)	Propofol (N=74)	P Value
Cardiac Index (ICU admission)	2.9 ± 0.7	2.5 ± 0.5	< 0.01
Cardiac Index (ICU discharge)	2.5 ± 0.4	2.6 ± 0.5	0.55
Atrial Fibrillation, n (%)	7 (10)	3 (4)	0.19
Inotrope, n (%)	32 (48)	31 (42)	0.50
Norepinephrine, n (%)	29 (43)	27 (36)	0.49
Vasopressin, n (%)	11 (16)	4 (5)	0.05
Troponin (12 hr)	3.2 (1.7-6.5)	3 (2.1-5.4)	0.65
Readiness to extubation, min	135 (95-200)	215 (150-280)	< 0.001
Extubation time, min	182 (140-255)	292 (210-420)	< 0.001
Readiness to Discharge time, min	870 (490-1710)	895 (670-1485)	0.22
ICU Discharge time, min	1510 (1340-2990)	1493 (1255-2690)	0.34
HLOS, days	6 (5-7)	6 (5-8)	0.79

	Volatile (N=67)	Propofol (N=74)	P Value
Shivering, n (%)	6 (10)	9 (13)	0.78
Nausea + Vomiting, n (%)	11 (19)	6 (9)	0.12
Pain Score 1 hr post extubation	4.1 ± 3.1	3.9 ± 3.0	0.80
4 hr post extubation	3.4 ± 2.4	[illegible]	0.54
Pain Score, POD 1 Rest	2.8 ± 2.1	2.9 ± 2.3	0.86
Cough	5.4 ± 2.5	6.0 ± 2.3	0.16
Analgesic Requirement, mg/12-24 hr			
Morphine	8.5 ± 8.2	5.9 ± 5.6	0.14
Acetaminophen	414.1 ± 745.4	528.9 ± 857.1	0.58
Indomethacin	15.3 ± 40.7	18.9 ± 38.6	0.27
% patients treated with Morphine	83.1	79	0.15
Acetaminophen	39.3	34.5	0.26
Indomethacin	15.1	7.4	0.57
RASS POD 0	0.46 ± 1	0.79 ± 1.2	0.24
POD 1	0.81 ± 1	0.72 ± 1.1	0.56
POD 2	0.87 ± 1	0.97 ± 1	0.64

Volatiles for longer-term ICU sedation ?

Long-term sedation in intensive care unit: a randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam.

Mesnil M, Capdevila X, Bringuier S et al. *Inten Care Med 2011; 37: 933*

- N=60, adult MSICU patients
- Sevoflurane vs. Propofol vs. Midazolam duration 96 h

	Sevoflurane N=19	Propofol N=14	Midazolam N=14
Wakeup time, mins*	18.6 +/- 11.8	91.3 +/- 35.2	260.2 +/- 150.2
Extubation delay, mins*	33.6 +/- 13.1	326.11 +/- 360.2	599.6 +/- 586.6
% Time with Ramsay score 3-4	75 (55-94)	75 (50-90)	70 (50-90)
No. hypnotic dose changes/day*	1.5 (0-2.5)	5 (4-8.5)	3.5 (2-5)
Pain score end sedation*	1 (0-1)	2.5 (1-5)	2 (2-3)
Morphine consumption / 24hrs, mg*	20 (4.5-30)	40 (30-60)	76 (55-111)
% vasopressor support*	35	48	42

*P<0.05

- No changes renal/liver function
- ↓ morphine consumption in sevoflurane group.....? NMDA antagonist

Impact upon survival?

Bellgardt et al 2015: Risk adjusted analysis 200 surgical ICU patients, Isoflurane Vs. propofol/midazolam > 96h (2005-2010)

	Odds ratio	95% CI	*P*
Primary outcome			
Hospital mortality			
Crude	0.39	(0.22 to 0.71)	0.002
Adjusted	0.35	(0.18 to 0.68)	0.002
Secondary outcome			
365-day mortality			
Crude	0.45	(0.25 to 0.82)	0.009
Adjusted	0.41	(0.21 to 0.81)	0.010

In-hospital mortality: 40% Iso vs. 63% pfl/mid, OR 0.35 (95% CI 0.18-0.68, p=0.002)

1 yr mortality: 50% Iso vs. 70% pfl/mid OR 0.41 (95% CI 0.21-0.81, p=0.010)

Bellgardt M et al. Eur J Anaesth 2015; 32:1

Impact on delirium?

?

- ↓ Post-extubation hallucinations
- No significant difference in post extubation agitation, memory or psychometric tests

Meiser A et al. BJA 2003; 90: 273; Hellstrom J et al. Scand Cardiovasc J 2012; 46: 262
Mesnil M et al. Inten Care Med 2011; 37: 933; Sackey P et al. Crit Care Med 2008; 36: 80

Practical & Safety Considerations of Using Volatile Agents in the ICU

ICU Delivery of Volatile Agents

1. Specialized equipment and set-up
2. Off-label use of volatiles
3. Atmospheric pollution
4. Cultural acceptance + training personnel

Volatile Delivery Systems

Anesthesia Machine

Anesthesia Conserving Device
AnaConDa

Ventilators
Servo900
Zeus desk-top
Cicerco

- Miniature vaporizer
- Compatible with any ICU ventilator
- Gas Sampling port for end tidal gas monitoring
- Volatile (isoflurane + sevoflurane) infused via syringe driver 1-5 ml/hr
- Efficiency > 90%
- Daily replacement
- Health Canada approved device

Device Limitations

- Tidal ventilation > 350 ml + re-breathing
- Secretions

Mirus

- Volatile delivery (Isoflurane, Sevoflurane, Desflurane)
- Bedside gas analyzer
- Automated target control of end-tidal gas concentration

Safety: Minimizing ICU Atmospheric Pollution

Acceptable occupational exposure limits

Volatile Agent	Long term Exposure Limit (Time weighted average, 8 hours) in ppm		
	UK/Europe	Canada	USA
Isoflurane	50	2	2
Sevoflurane	-	-	2
Halothane	10	2	2
Nitrous Oxide	100	25	25

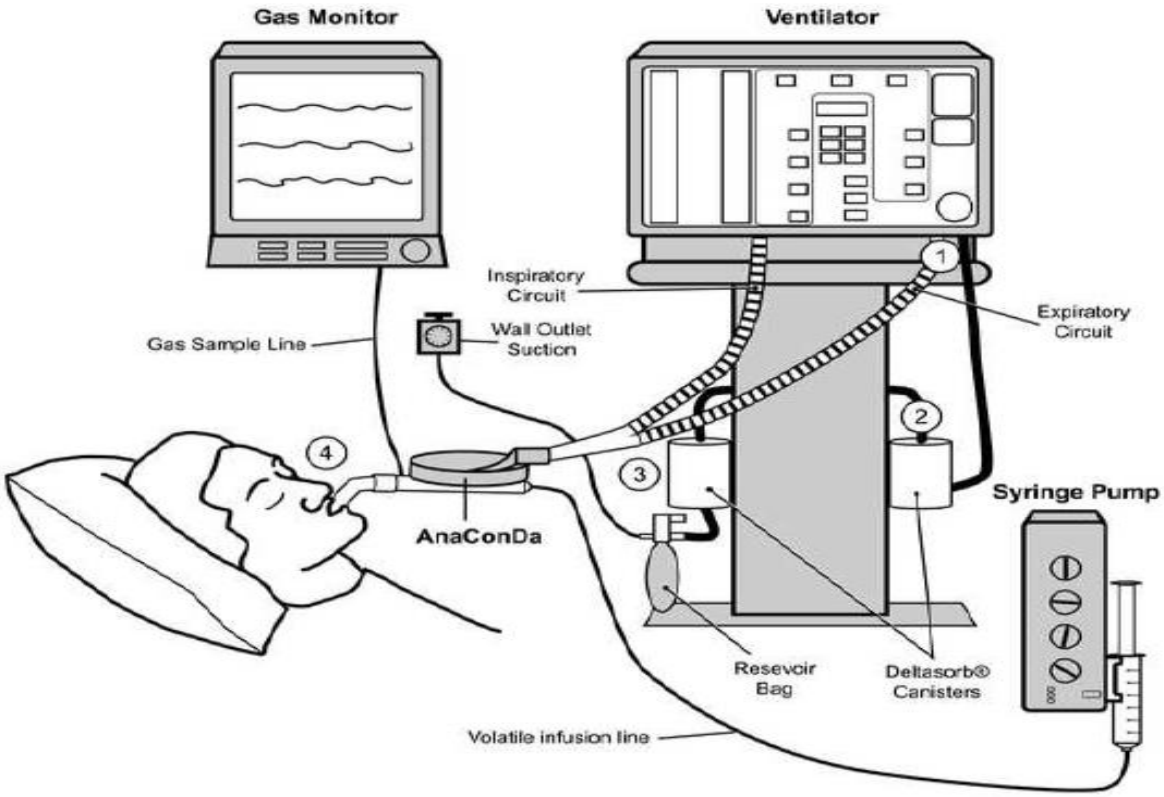
Minimizing ICU Atmospheric Pollution

1. Room air exchanges

2. Passive Gas Scavenging
   - Charcoal adsorbed (Contrafuran, Cardiff Aldasorber, Novasorb)
   - Canister saturation detected upon weight gain
   - Effective: Isoflurane infused 96 hr, atmospheric levels < 1ppm

3. Active scavenging

Toronto Experience



Atmospheric volatile concentration points of measurement

1 Expiratory port
2 Post 1st Deltasorb
3 Post 2nd Deltasorb
4 Patient head

2 Deltasorb canisters linked in series from ventilator expiratory port to wall suction

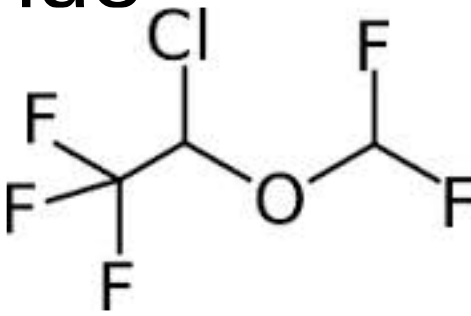
The scavenging of volatile anesthetic agents in the cardiovascular intensive care unit environment: a technical report.

Pickworth T, Jerath A, Wasowicz M et al. *Can J Anesth 2013; 60: 38*

Patient Number	Volatile Used	Expiratory Limb	Post 1st Deltasorb	Post 2nd Deltasorb	Room atmosphere
1	Sevoflurane	32	10	8	0
2	Isoflurane	0	0	0	0
3	Isoflurane	5	2	1	0
4	Sevoflurane	18	8	4	1
5	Isoflurane	1	1	1	0
6	Sevoflurane	1	0	0	0
7	Sevoflurane	10	1	2	0
8	Isoflurane	4	4	1	1
9	Sevoflurane	1	1	1	1
10	Sevoflurane	10	5	3	1
Mean +/- St Dev		**8.2 +/- 10.1**	**3.2 +/- 3.5**	**2.1 +/- 2.4**	**0.4 +/- 0.5**

Concentrations measured in parts per million using InfraRan, multigas infrared vapor analyzer (Wilkins Enterprise Inc. Massachusetts, USA)

Safety: Volatile associated Fluoride Nephrotoxicity?



- Historical Data
  - Methoxyflurane associated polyuric renal failure with fluoride > 50 umol/L
- Modern agents
  - No association between serum fluoride levels and renal function
  - ? safe threshold

Osborne et al. Inten Care Med 1996; 22: 677; Mesnil M et al. Int Car Med 2011; 37:933
Jerath A et al. J Crit Care 2015; 30: 843

Safety

- Risk of malignant hyperthermia (1-5/200,000)

- ? Pediatric Neurotoxicity
  - Animal Data: neurodegeneration + apoptosis
  - Human Translations: Mixed data, numerous confounders
  - Current Studies: PANDA + GAS trial

Chiao S et al. Brain Sci 2014; 4: 273; Wilder RT et al. Anesthesiology 2009; 110: 796
Sun LS et al. J Neurosurg Anesthesiol 2012; 24: 382

Summary

- Novel group of agents with unique pharmacokinetic properties
- Volatiles can be easily delivered outside of the operating room
- ICU scavenging systems facilitate safe delivery
- Future role as ICU sedatives?

Thank You!

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