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INTRODUCING INHALED SEDATION

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SEDATION IN CRITICALLY ILL PATIENTS

CHAPTER 1

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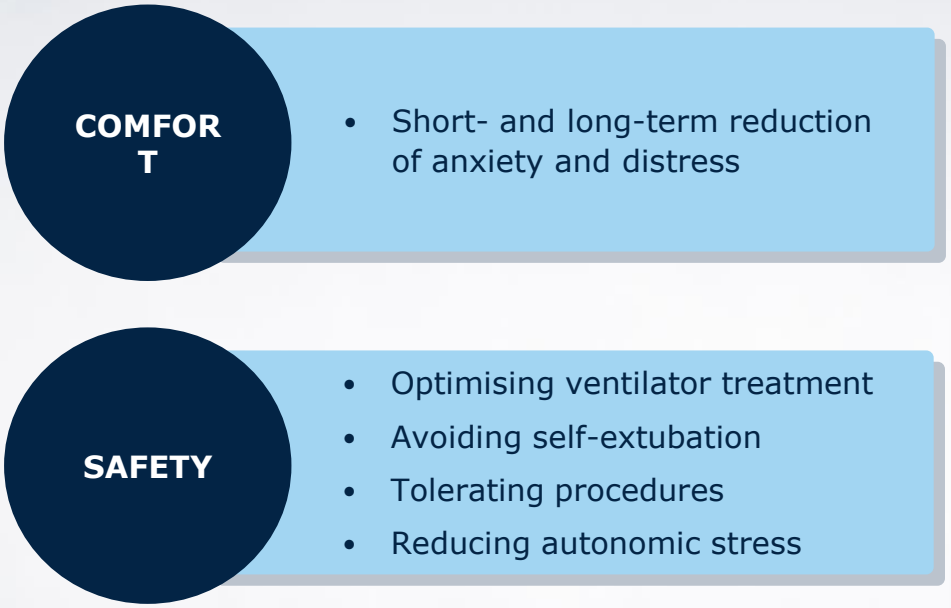
Key role of sedation

Critically ill patients treated with invasive mechanical ventilation very often need to be sedated for their **comfort** and **safety**.[1]



1. Hughes et al., Clin Pharmacol 2012.

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Common objectives in sedation recommendations

Sedation recommendations[1-3] developed from the Intensive Care medical societies of different countries have common objectives:

Limit long-term physical and psychological impact of ICU stay

Minimize ventilation duration and related complications

Limit side effects using lowest effective dose of sedative (best benefit-risk ratio)

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1. Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018). 2. Celiz-Rodriguez et al., Med Intensiva (Engl Ed) 2020 (Panamerican Guidelines 2020). 3. DAS-Task Force 2015, Ger Med Sci 2015 (German DAS Guidelines 2015).

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Challenges with current sedation strategies

Patient diversity

- Unpredictable PK and PD[1]
  - Chronic illness
  - Acute organ dysfunction
  - Advanced age
- Sedation needs change over time
- Development of drug tolerance[2]

Risk of iatrogenic harm

- Short-term risks of sedation
  - Hypotension, bradycardia[2]
  - Propofol infusion syndrome[3]
  - Withdrawal syndrome[2]
  - Delirium[4] and hallucinations[2]
- Long-term risks of sedation
  - Slow and unpredictable awakening, prolonged mechanical ventilation and ICU stay[2]
  - Cognitive dysfunction[4]
  - Post-traumatic stress disorder[2]

Finding the right balance

Oversedation[1,4]

vs

Undersedation[5]

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1. Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018).
2. Jerath et al., Am J Resp Crit Care Med 2016. 3. Krajcova et al., Crit Care 2015.
4. Pandharipande et al., JAMA 2007. 5. Olsen et al., N Engl J Med 2020.

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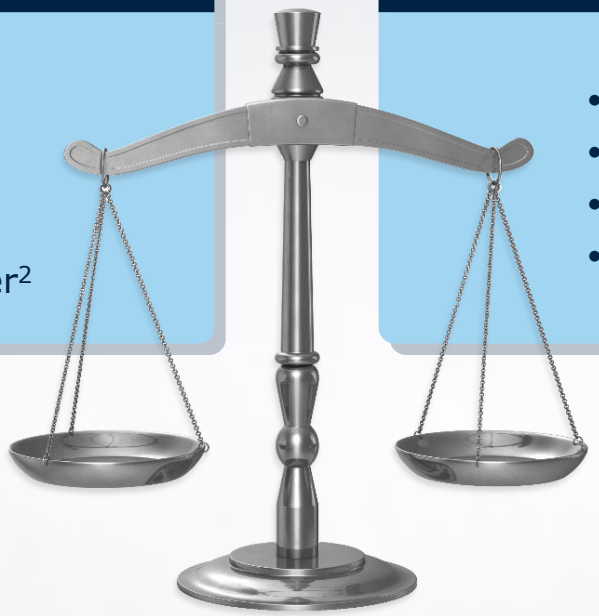
Consequences of over- and undersedation in mechanically ventilated patients

Undersedation

- Hypertension, tachycardia[1]
- Agitated delirium[1]
- Patient safety risks[1,2]
- Ventilator asynchrony[1]
- Post-traumatic stress disorder[2]



Oversedation

- Hypotension[1]
- Prolonged ventilator time[1]
- Complications to critical care[1]
- Delirium[3]

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1. Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018). 2. Franks et al., Ann Am Thorac 2021. 3. Pandharipande et al., Anesthesiology 2006.

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Proposed strategies to avoid iatrogenic harm

Avoid benzo-diazepines

- Benzodiazepines are associated with the development of delirium[1]
- Benzodiazepine infusions lead to prolonged wake-up[2]
- Guidelines recommend non-benzodiazepine sedation strategies[2]

Daily wake-up

- Daily interruption of IV sedatives and opioids decreases residual sedation, leading to shorter ventilator time and ICU stay[3]
- Guidelines recommend SAT together with SBT[4], unless patient is lightly sedated

Light sedation

- Light IV sedation is as good as daily interruption[5]

SAT=Spontaneous Awakening Test. SBT=Spontaneous Breathing Test.

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1. Pandharipande et al., Anesthesiology 2006. 2. Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018). 3. Kress et al., N Engl J Med 2000. 4. Girard et al., Lancet 2008. 5. Mehta et al., JAMA 2014.

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ABCDEF bundles

Society of Critical Care Medicine: The ABCDEF Bundle elements individually and collectively can help reduce delirium, improve pain management and reduce long-term consequences for adult intensive care unit (ICU) patients.

A ssess, prevent and manage pain

B oth Spontaneous Awakening Test (SAT) and Spontaneous Breathing Test (SBT)

C hoice of analgesia and sedation

D elirium – assess, prevent, manage

E arly mobility and exercise

F amily engagement

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Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018).

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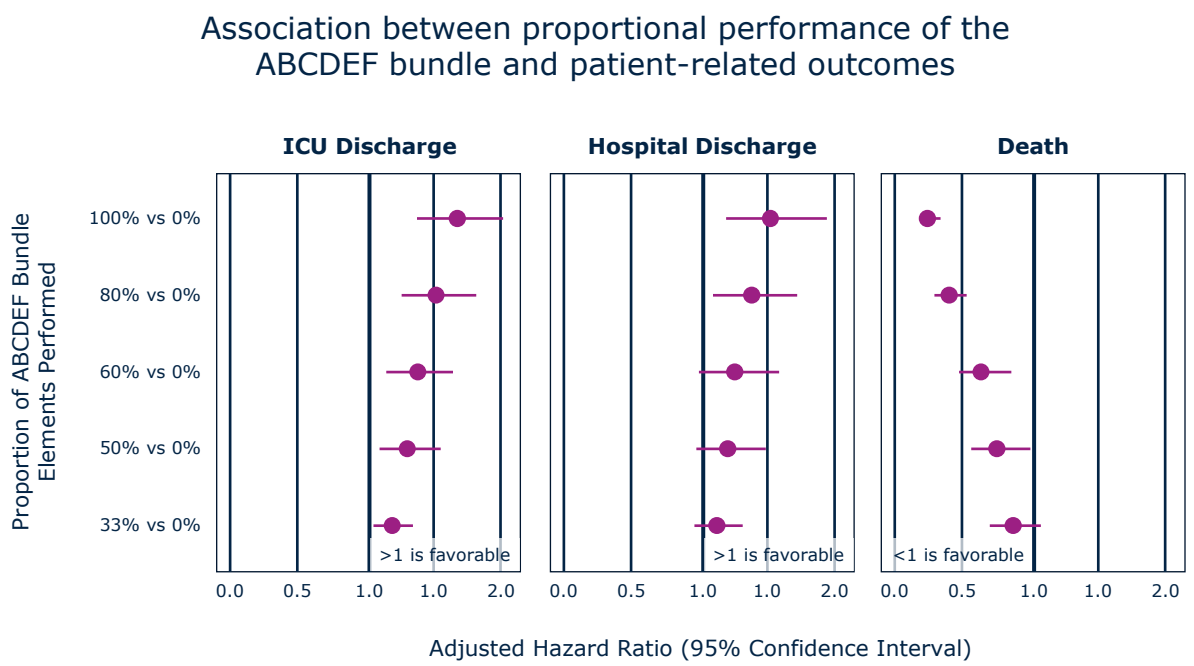
Effect of ABCDEF bundle adherence



ABCDEF bundle performance showed significant and clinically meaningful improvements in outcomes including:

- Survival
- Mechanical ventilation use
- Coma and delirium
- Restraint use
- ICU readmissions
- Post-ICU discharge disposition

Pun et al., Crit Care Med 2019.

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The ”No/Light sedation” approach

- Motivated by justified concerns regarding iatrogenic harm caused by oversedation.
- Sedation depth has been found to predict increased risk of death, delirium, and delayed time to extubation.[1]
- If a patient is awake, comfortable and safe, don’t start any sedation.
- Early trials with small sample sizes[2,3] suggested the feasibility and safety of the no/light sedation approach and hinted some benefits compared to usual care, leading to larger RCTs being performed.

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1. Shehabi et al., Crit Care Med 2018. 2. Strøm et al., Lancet 2010. 3. Shehabi et al., Crit Care Med 2013.

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Potential challenges with the ”No/Light sedation” approach

- Recent publications[1-3] highlight the challenge in using a one-size-fits-all approach.
- No/light sedation not suitable for, and/or difficult to achieve in, a significant proportion of patients.[1,2]
- Three large RCTs[1-3] on no/light sedation found no improvements in terms of:
  - Mortality at 90 days
  - Ventilator-, coma/delirium- or ICU-free days
- Concerns regarding patient comfort and safety with no/light sedation approach:
  - Higher risk of self-removal of ET-tube, GI-tube or arterial line[2]
  - Increased nurse-to-patient ratio needed to manage non-sedated patients in distress[2]
  - Increased use of restraints on non-sedated patients[3]

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1. Shehabi et al., N Engl J Med 2019. 2. Olsen et al., N Engl J Med 2020 (Electronic supplementary material). 3. Hughes et al., N Engl J Med 2021.

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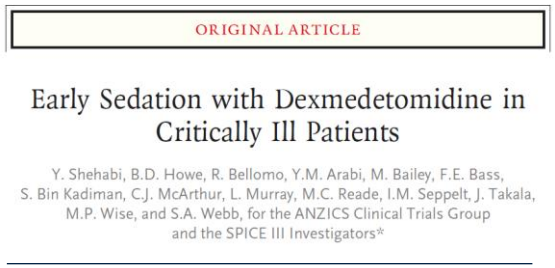
Studies on the ”No/Light sedation” approach

Recent publications highlight the challenge in using a one-size-fits-all approach

1


The NEW ENGLAND JOURNAL of MEDICINE

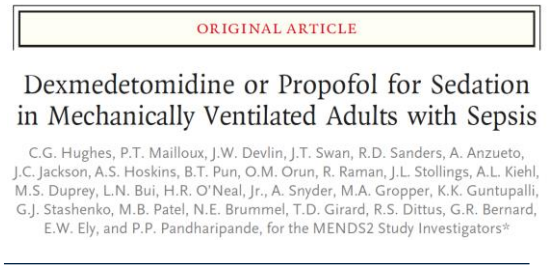
ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

- No difference in 90-day mortality between dexmedetomidine or usual care
- ~50% of patients *needed* deeper sedation (RASS -3 or deeper) during the first 2 days
- >25% patients needed deeper sedation during the first week

2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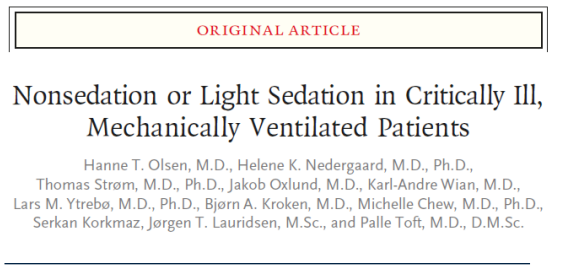
Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

C.G. Hughes, P.T. Mailloux, J.W. Devlin, J.T. Swan, R.D. Sanders, A. Anzueto, J.C. Jackson, A.S. Hoskins, B.T. Pun, O.M. Orun, R. Raman, J.L. Stollings, A.L. Kiehl, M.S. Duprey, L.N. Bui, H.R. O'Neal, Jr., A. Snyder, M.A. Gropper, K.K. Guntupalli, G.J. Stashenko, M.B. Patel, N.E. Brummel, T.D. Girard, R.S. Dittus, G.R. Bernard, E.W. Ely, and P.P. Pandharipande, for the MENDS2 Study Investigators*

- No difference in outcomes in patients who received dexmedetomidine compared with propofol
- Despite targeting light sedation a large proportion of patients needed deeper sedation during the first week

3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ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

Hanne T. Olsen, M.D., Helene K. Nedergaard, M.D., Ph.D., Thomas Strøm, M.D., Ph.D., Jakob Oxlund, M.D., Karl-Andre Wian, M.D., Lars M. Ytrebø, M.D., Ph.D., Bjørn A. Kroken, M.D., Michelle Chew, M.D., Ph.D., Serkan Korkmaz, Jørgen T. Lauridsen, M.Sc., and Palle Toft, M.D., D.M.Sc.

- No difference in 90-day mortality between patients on no sedation compared to light sedation
- Higher risk of self-removal of ET-tube, GI-tube or arterial line in non-sedated patients

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1. Shehabi et al., N Engl J Med 2019. 2. Hughes et al., N Engl J Med 2021.
3. Olsen et al., N Engl J Med 2020.

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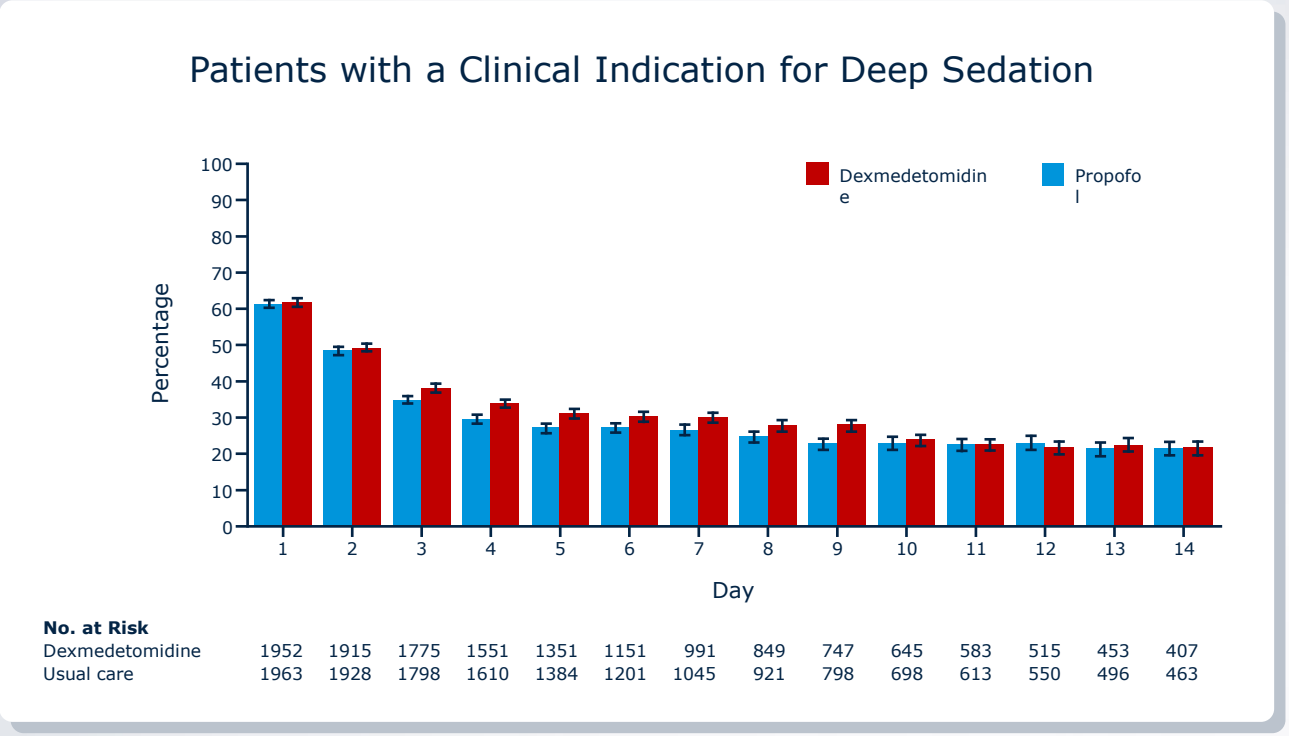
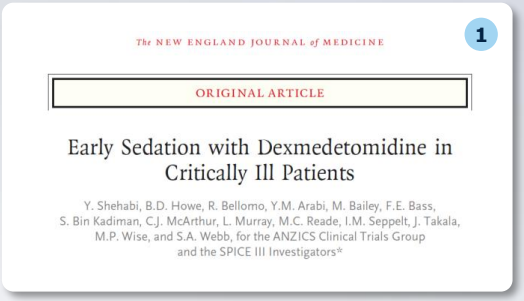
No/Light sedation is not deemed suitable for all patients

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- Target sedation level: RASS **−2 to +1**
- Patients in need for deeper sedation (RASS -3 or deeper)
  - First 2 days: ~50%
  - First week: >25%
- 75% of patients on dexmedetomidine needed supplemental sedatives the first two days to achieve the sedation level needed

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Shehabi et al., N Engl J Med 2019.

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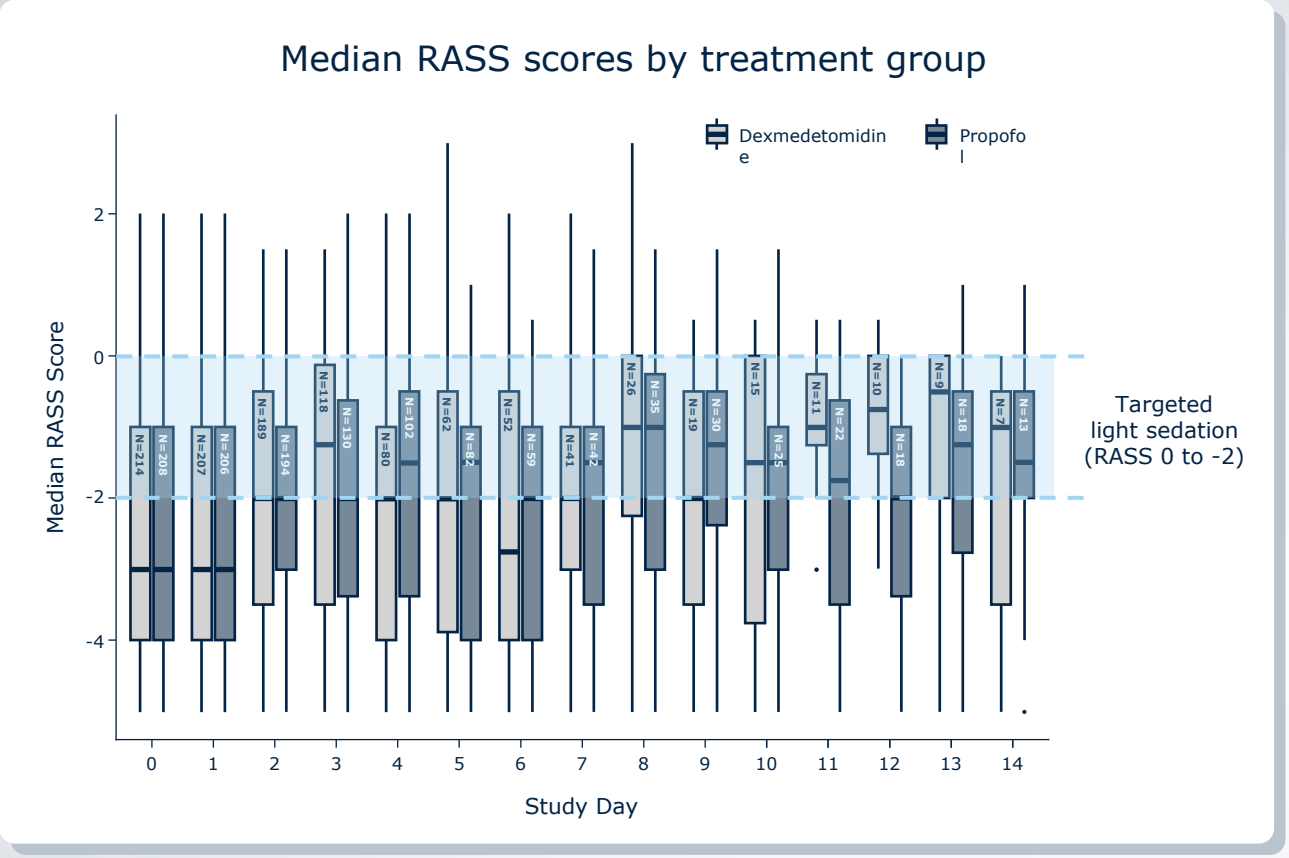
No/Light sedation might be hard to achieve

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- Despite targeting light sedation (RASS 0 to -2), a large proportion of patients required deeper sedation during the first week

Hughes et al., N Engl J Med 2021.

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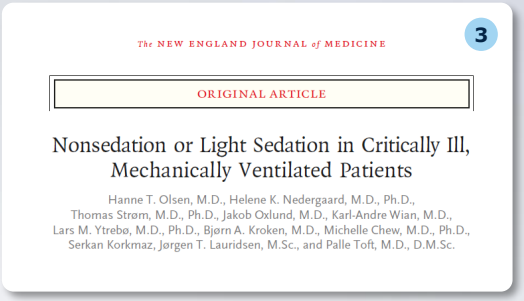
No sedation - more risk than benefit?

	Non-sedated	Sedated
Self-extubation (& re-intubation within 24h)	**8.9 %**	**4%**
Self-removal of other equipment (GI tube, arterial line)	**15.2 %**	**9.1%**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- Higher risk of self-removal of ET-tube, GI-tube or arterial line in non-sedated patients.
- Self-extubation and removal of other equipment were common **despite a 1:1 nurse-to-patient ratio** in most participating ICUs.

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Olsen et al., N Engl J Med 2020 (Electronic supplementary material).

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Proposed medical properties of the ideal sedative agent

The 'ideal sedative agent' should possess the following qualities:

- Sedative, analgesic and anxiolytic properties[1,3]
- Rapid onset and offset of action[1,3]
- Predictable dose-response relationship[1]
- Few side effects[1]
- Organ-independent elimination[2]
- No active metabolites[2,3]
- No drug accumulation[1,3]
- Minimal drug interactions[1,3]

Inhaled sedation (isoflurane/ sevoflurane) has been proposed as "the ideal sedative agent." [4-6]

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1. Ostermann et al., JAMA 2000. 2. Hughes et al., Clin Pharmacol 2012. 3. https://www.ics.ac.uk/Society/Guidance/PDFs/Analgesia_and_Sedation. 4. Spencer et al., Int Care Med 1992. 5. Kong et al., BMJ 1989. 6. Hendrickx et al., J Clin Monit Comput 2018.

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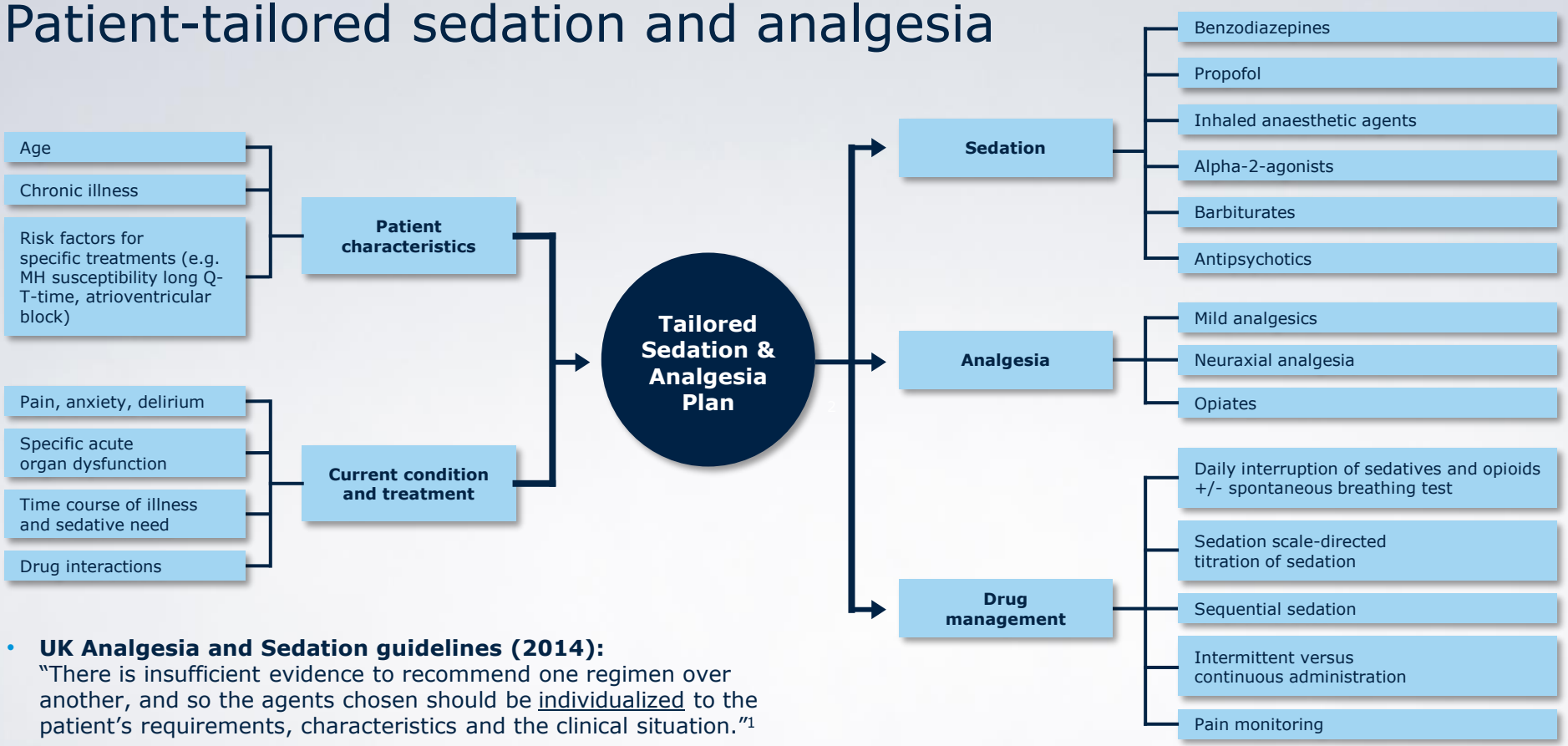
Patient-tailored sedation and analgesia



- **UK Analgesia and Sedation guidelines (2014):**
  "There is insufficient evidence to recommend one regimen over another, and so the agents chosen should be individualized to the patient's requirements, characteristics and the clinical situation."[1]
- There is no "one-size-fits-all" solution[2]

1. https://www.ics.ac.uk/Society/Guidance/PDFs/Analgesia_and_Sedation.
2. Sackey et al., Anesthesiology 2010.

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Current sedative agents

	MIDAZOLAM[1]	PROPOFOL[2]	DEXMEDETOMIDINE[3-5]	ISOFLURANE[6-9]	SEVOFLURANE[9,10]
Drug class	benzodiazepine	GABA agonist	alpha-2 receptor agonist	fluorinated ether	fluorinated ether
Metabolisation	40-60%	66%	95%	0.2%	2-5%
Degradation metabolite	α-hydroxymidazolam	Glucuronides	Glucuronides	Trifluoracetic acid, fluorides	Fluorides, hexafluoroisopropanol
Active metabolite	Yes	No	No	No	No
Elimination	60-80% renal	88% renal	90% renal	Pulmonary exhalation	
Duration of action					
$T_{1/2}$ context-sensitive	1.5-3.0 h (single shot)	1.5-12.4 h	1.9-2.5 h	< 5 min	< 5 min
80% decrement time	3-12 h (up to several days)	3.5 h-3 d	3.7 h	30-35 min	< 8 min

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1. Nordt et al., J Emerg Med 1997. 2. Trapani et al., Curr Med Chem 2000. 3. Weerink et al., Clin Pharmacokin 2017. 4. Iirola et al., Crit Care 2011. 5. Venn et al., Br J Anaesth 2002. 6. Mazze et al., Anesthesiology 1974. 7. Holaday et al., Anesthesiology 1975. 8. Kharasch et al., Anesthesiology 1999. 9. Bailey et al., Anesth Analg 1997. 10. Behne et al., Clin Pharmacokinet 1999.

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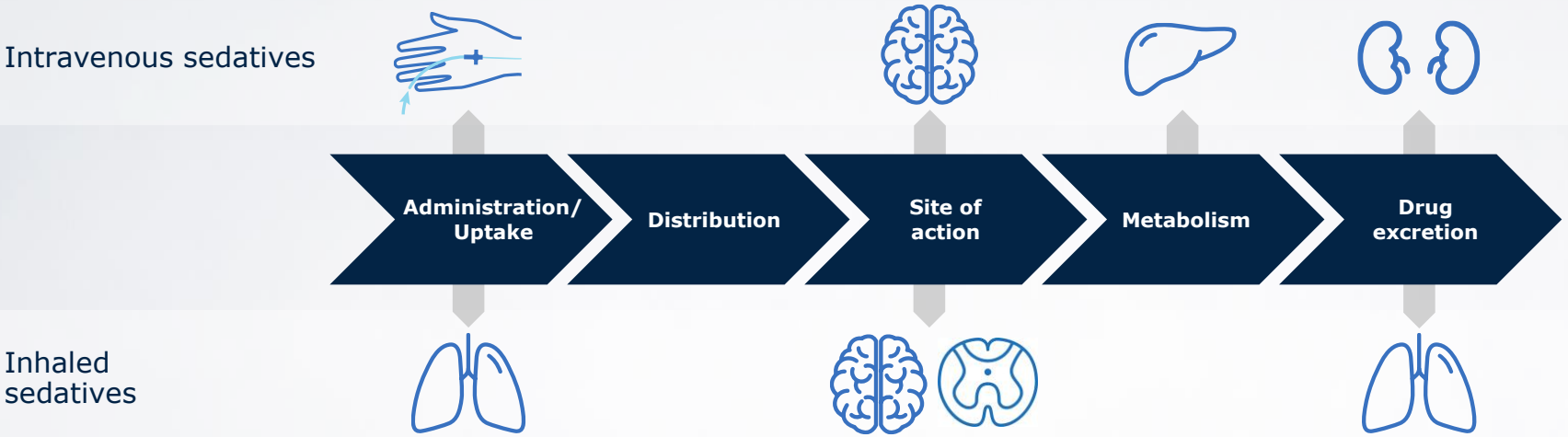
Pharmacokinetics of intravenous vs inhaled sedatives

Elimination of intravenous sedatives relies on adequate hepatic and renal function[1]

Hepatic and renal function are often impaired in ICU patients[2], leading to slow elimination[1], risk of drug accumulation and oversedation[3-8]



Elimination of inhaled sedatives is independent of hepatic and renal function[9,10]

Inhaled sedation works even in severe ARDS on ECMO[11,12]

1. Jerath et al., Anesth Analg 2017. 2. Vincent et al., Crit Care Med 2006. 3. Shelly et al., Eur J Anaesthesiol 1991. 4. Devlin et al., Crit Care Med 2018 (PADIS Clinical Practice Guidelines 2018). 5. Barr et al., Anesthesiology 2001. 6. Jerath et al., 2016. 7. Shafer et al., Crit Care Med 1998. 8. Sackey et al., Crit Care Med 2004. 9. Eger, Br J Anaesth 1984. 10. Lu et al., Pharmacology 2008. 11. Meiser et al., Respir Care 2018. 12. Rand et al., J Artif Organs 2018.

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History of Inhaled Sedation

1846
First use of ether for general anaesthesia

1950's
First use of halothane for general anaesthesia

1979
Isoflurane approved for general anaesthesia in the United States

Late 1980's
First RCT on **isoflurane for sedation** of patients in the ICU[1]

1990's
Sevoflurane introduced for general anaesthesia in Japan

2005
First medical **device AnaConDa*** for administration of inhaled sedatives is CE marked

Clinical experience of inhaled sedation published in >50 peer-reviewed publications

2021
Largest RCT on inhaled sedation published, the **Sedaconda study**[2]

2021
First drug approved for inhaled sedation in Europe

*Currently called Sedaconda® ACD (Anaesthetic Conserving Device)

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1. Kong et al., BMJ 1989. 2. Meiser et al., Lancet Resp Med 2021.

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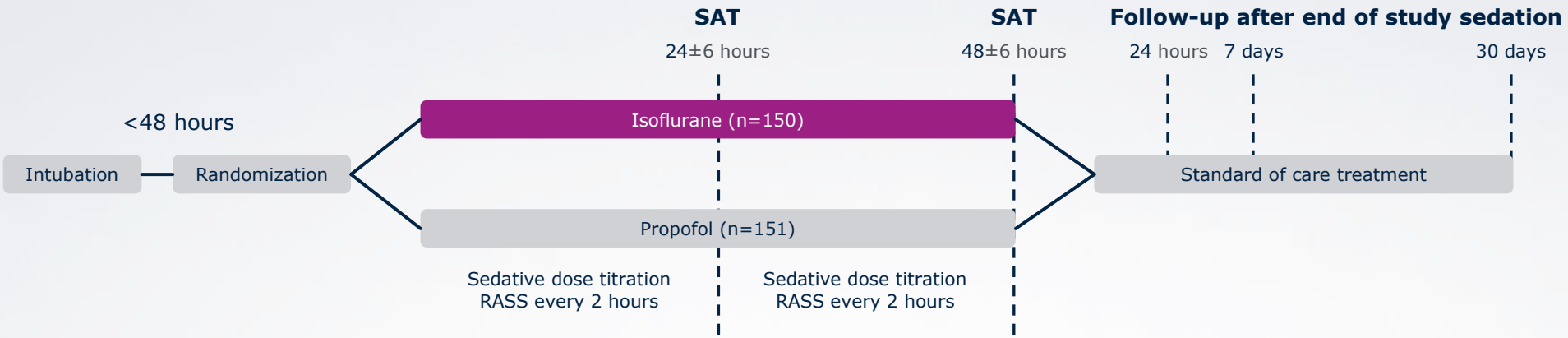
The Sedaconda study



- The largest prospective trial to date on inhaled sedation
- A phase 3, randomised, controlled, open-label, multicentre, parallel-group, non-inferiority trial designed to meet the European regulatory requirements for approval
- The study objective was to demonstrate the efficacy and safety of isoflurane for sedation in invasively ventilated intensive care unit (ICU) patients using the Sedaconda ACD delivery device
- The study demonstrated non-inferior sedation efficacy of isoflurane compared to propofol

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Meiser et al., Lancet Resp Med 2021.

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Isoflurane for Inhaled Sedation in the ICU

- Sedaconda® (isoflurane) is currently the only drug approved for the indication of inhaled sedation of adults in the ICU.[1]
- Metabolised at a very low rate (0.2%)[2]
  - Elimination independent of liver or renal function[3]
- Tissue accumulation in muscle and fat during sedation is clinically insignificant[4]
- Elimination is via the lungs (>99%)[3,5,6]
  - Wake-up time within one hour after days of sedation[4,7,8]

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1. Sedaconda SmPC, 2021. 2. Eger, Br J Anaesth 1984. 3. Holaday et al., Anesthesiology 1975. 4. Spencer and Willatts, Intensive Care Med 1992. 5. Kharasch et al., Anesthesiology 1999. 6. Mazze et al., Anesthesiology 1974. 7. Kong et al., BMJ 1989. 8. Sackey et al., Crit Care Med 2004.

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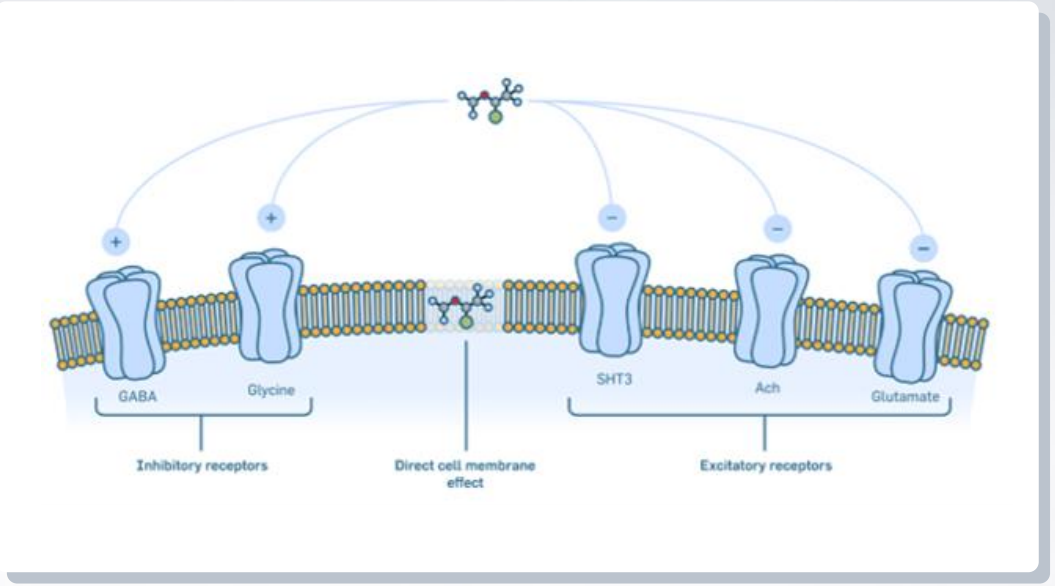
Pharmacodynamics - How do inhaled sedatives work?

Multiple mechanisms of action[1-4]

- Potentiation of inhibitory receptors
- Inhibition of excitatory receptors
- Direct cell membrane effects



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1. Campagna et al., N Engl J Med 2003. 2. Herold et al., J Gen Physiol 2014.
3. Wu et al., Anesthesiology 2004. 4. Herold et al., Eur Biophys J 2017.

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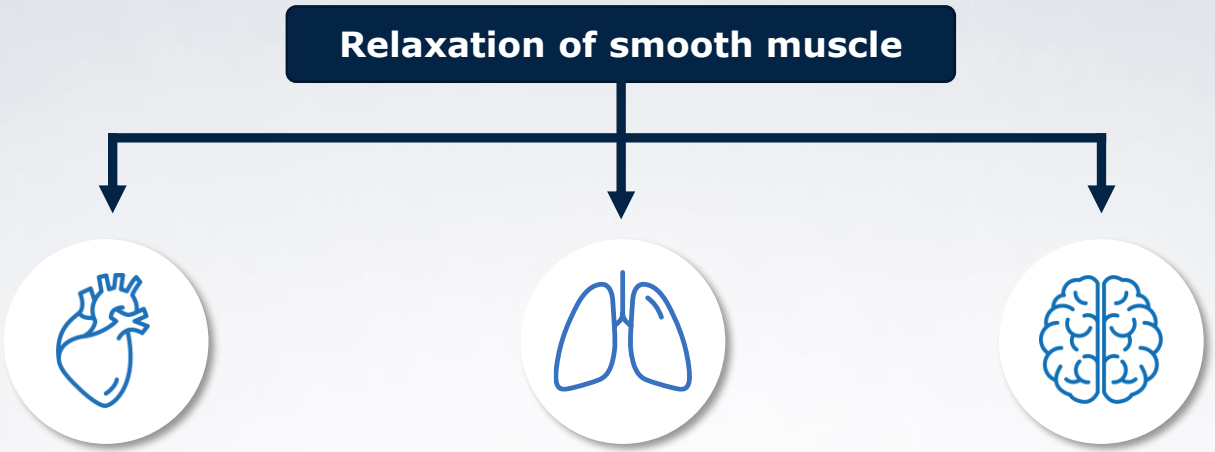
Pharmacodynamics of isoflurane, besides sedation



Effect	Peripheral vasodilation[1]	Bronchodilation[2]	Cerebral vasodilation[3]
Potential side effect	→ Reduces blood pressure		→ May increase intracranial pressure

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1. Crystal, J Anesth Hist 2017. 2. Turner et al., Respir Care 2012. 3. Basil et al., Anesthesiology 1999.

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EFFICACY OF INHALED SEDATION

CHAPTER 2

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Inhaled sedatives – Fast onset of sedation

Sedation efficacy

Administered via the airways and lungs

Rapid alveolar uptake

Delivered via the bloodstream to the brain

Fast onset of sedation

- No significant concerns of drug tolerance
- Dose requirements do normally not increase over time

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Jerath et al., Am J Respir Crit Care Med 2016.

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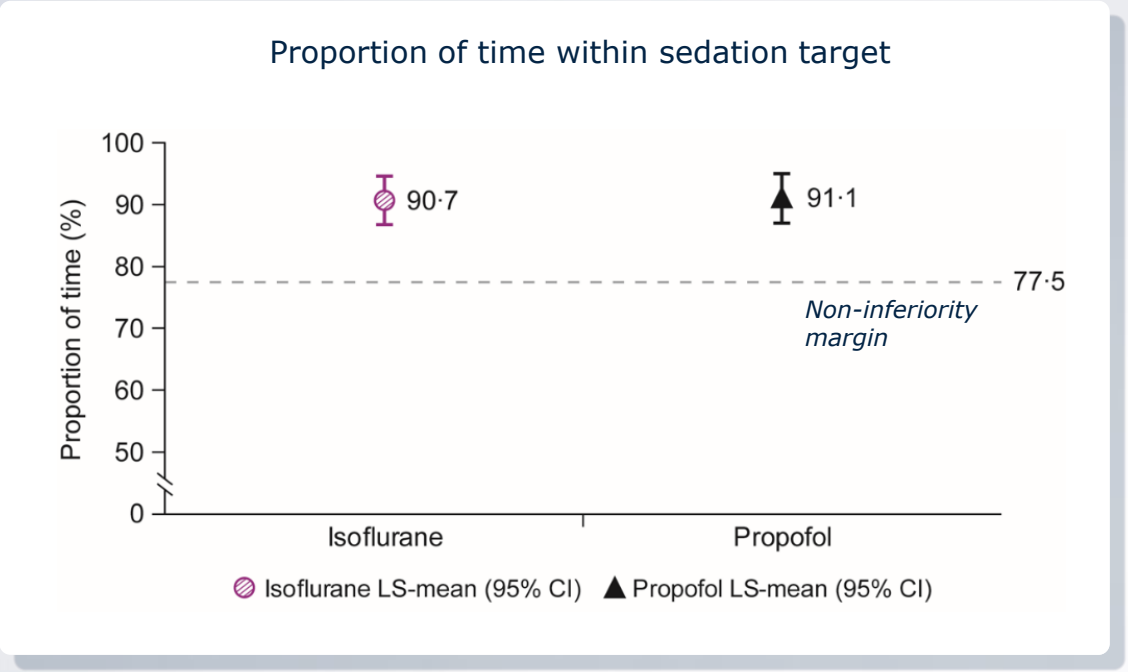
Sedation efficacy isoflurane vs propofol

The Sedaconda study:
Comparable time spent in the target RASS range without rescue sedation



RASS=Richmond Agitation–Sedation Scale

Proportion of time within the sedation target range:

- >90% in both groups
- Isoflurane non-inferior to propofol

Meiser et al., Lancet Resp Med 2021.

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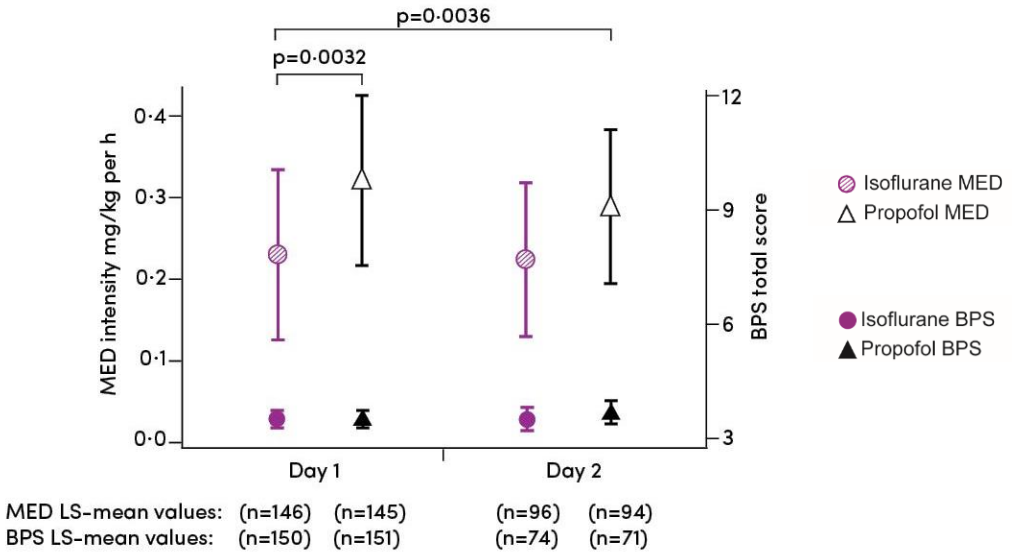
Lower opioid requirements with isoflurane

Opioid reduction

Morphine equivalent dose intensity and BPS during study sedation



MED=Morphine Equivalent Dose. BPS=Behavioural Pain Scale

- In the Sedaconda study, opioid dose intensity was **29% lower** in the isoflurane group compared to the propofol group.
- No signs of clinical pain issues in relation to opioid dose reduction, as indicated by BPS scores.

Meiser et al., Lancet Resp Med 2021.

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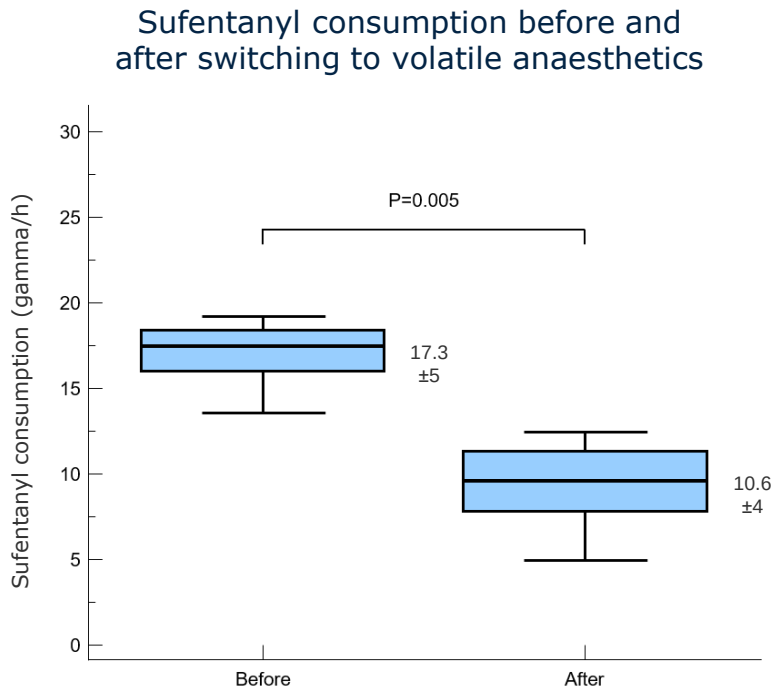
Opioid reduction in Covid-19 ARDS after switching from IV sedation to isoflurane

Opioid reduction



- Switch from midazolam to isoflurane in 11 mechanically ventilated Covid-19 patients.
- Sufentanyl consumption decreased significantly while the same analgosedation goal was reached.

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Ferrière et al., J Crit Care 2021.

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Opioid reduction with isoflurane[1]

Opioid reduction

- Inhaled anaesthetics have antinociceptive effects on the spinal cord[1,2] which may explain the reduced opioid needs with isoflurane.
- Lower opioid doses may lead to:
  - Gut mobility better preserved[3]
  - Spontaneous breathing preserved[1]
  - Risk of delirium decreased[4,5]

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1. Meiser et al., Lancet Resp Med 2021. 2. Collins et al., Trends Neurosci 1995. 3. Schug et al., Drug Safety 1992. 4. Clegg et al., Age Ageing 2011. 5. Dubois et al., Intensive Care Med 2001.

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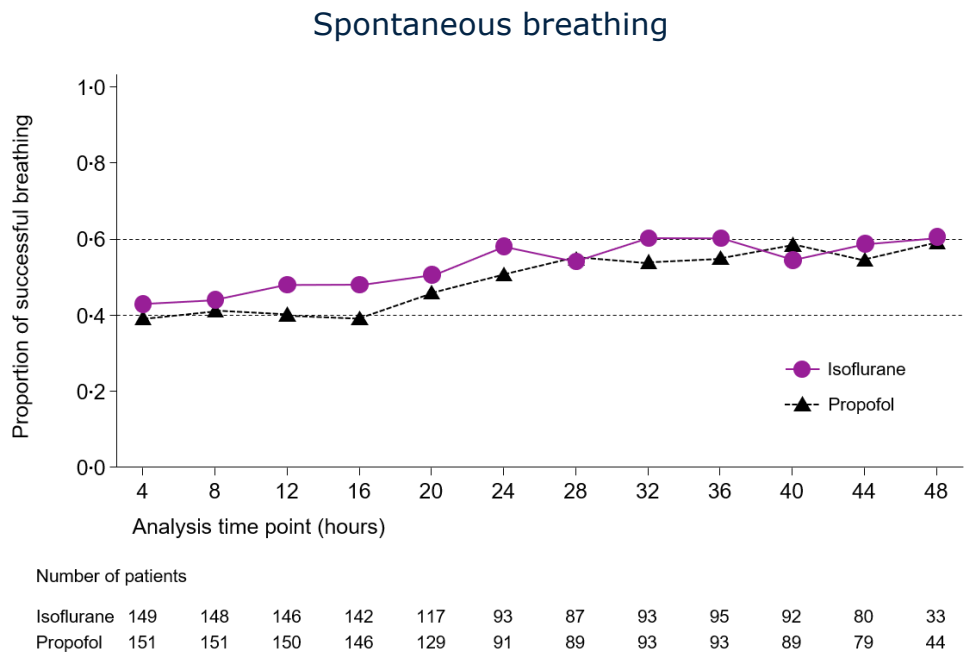
Spontaneous breathing more common with isoflurane



Estimated rate of spontaneous breathing in the Sedaconda study:

Day 1

- Isoflurane 50.3%
- Propofol 37.0%

} p=0.013

Day 2

- The difference favored isoflurane but did not reach statistical significance

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Meiser et al., Lancet Resp Med 2021.

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Spontaneous breathing preserves muscle function

- Spontaneous breathing prevents respiratory muscle fiber dysfunction[1,2]
- Preserved respiratory muscle function shortens ICU length of stay[3]
- Respiratory muscle weakness after mechanical ventilation is associated with one-year mortality[4]
- Augmented spontaneous breathing may recruit lung tissue in dependent areas[5]

> "Improvements in pulmonary gas exchange, systemic blood flow and oxygen supply to the tissue which have been observed when spontaneous breathing has been maintained during mechanical ventilation are reflected in the clinical improvement in the patient's condition."[3]

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1. Dres et al., Intensive Care Med 2017. 2. Goligher et al., Am J Respir Crit Care Med 2015. 3. Putensen et al., Curr Opin Crit Care 2006. 4. Medrinal et al., Crit Care 2016. 5. Putensen et al., Crit Care 2004.

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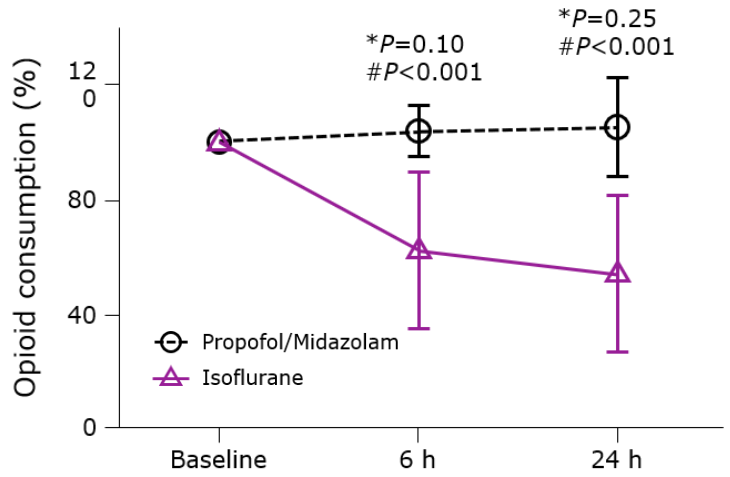
Isoflurane facilitated opioid reduction and spontaneous breathing in ARDS patients

Opioid reduction

Spontaneous breathing

Opioid consumption before and during isoflurane sedation compared with propofol/midazolam



	Propofol/ Midazolam *n* = 19	Isoflurane *n* = 19	*P*
SAPS II, points			
Before	43.2 ± 15.2	40.2 ± 9.6	.47
6 h	41.4 ± 14.9	39.2 ± 9.8	.61
24 h	42.6 ± 13.8	35.7 ± 10.2	.10
Remifentanil, µg/kg/min	n = 14	n = 16	
Before	0.22 ± 0.09	0.19 ± 0.10	.39
6 h	0.23 ± 0.10	0.10 ± 0.04*	.007
24 h	0.25 ± 0.09	0.09 ± 0.04*	< .001
Sufentanil, µg/kg/h	*n* = 5	*n* = 3	
Before	0.68 ± 0.59	0.46 ± 0.66	.64
6 h	0.68 ± 0.58	0.29 ± 0.45	.20
24 h	0.52 ± 0.55	0.29 ± 0.45	.38
Spontaneous breathing			
Before	3 (16)	2 (11)	.64
6 h	3 (16)	12 (63)	.003
24 h	3 (16)	17 (90)	< .001

Data are shown as mean ± SD.
**P* compared to baseline, *#P* compared to propofol/midazolam.

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Meiser et al., Resp Care 2018.

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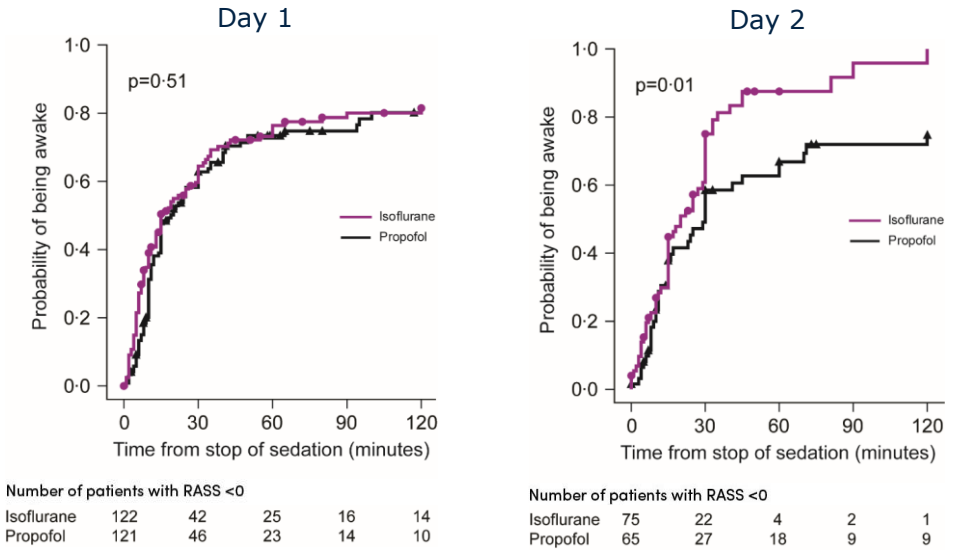
Shorter and more predictable wake-up time with isoflurane

Short time to wake-up

Time to wake-up during SAT



SAT = spontaneous awakening trial.

The Sedaconda study showed:

- Faster wake-up with isoflurane than propofol
  - Day 1
    - No statistically significant difference
  - Day 2
    - Isoflurane: 20 min (IQR 10-30 min)
    - Propofol: 30 min (IQR 11-120 min)
- Lower inter-individual variability with isoflurane (more predictable)

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Meiser et al., Lancet Resp Med 2021.

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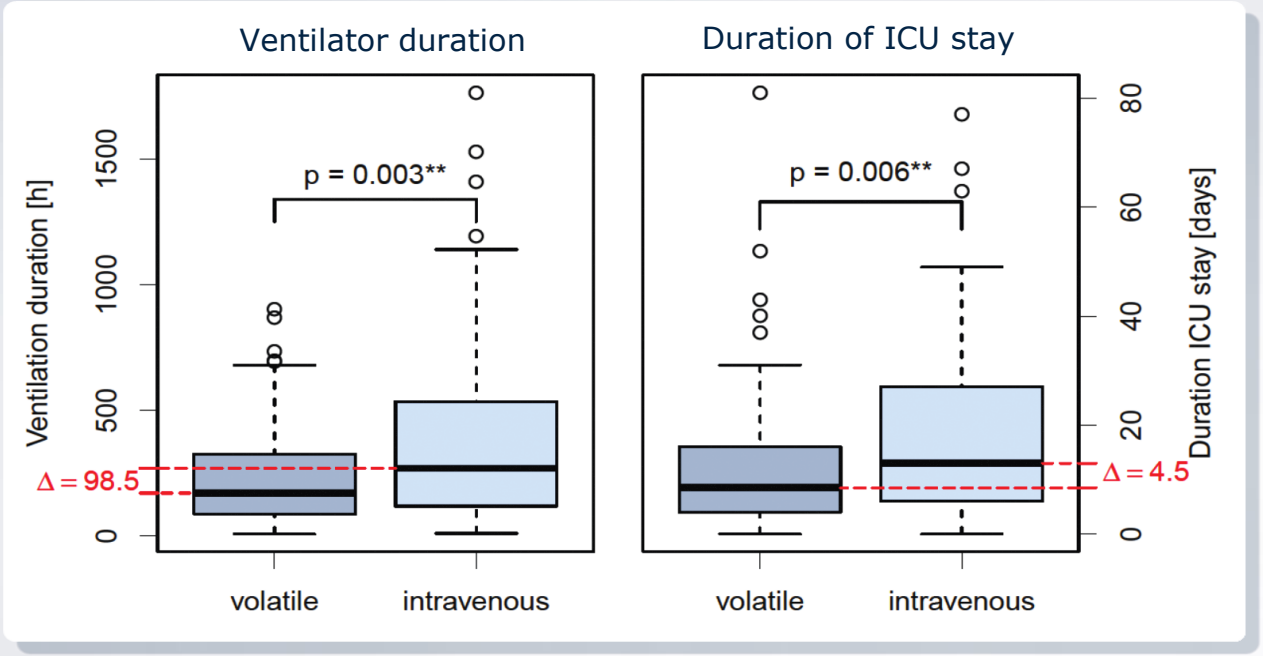
Shorter ventilator time and ICU stay with isoflurane in cardiac arrest patients

Shorter stay in ICU



Isoflurane sedation was associated with:

- Shorter ventilator time (p=0.003)
- Shorter ICU stay (p=0.006)

Krannich et al., Crit Care Med 2017.

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Fast cognitive recovery

1

Isoflurane compared with midazolam for sedation in the intensive care unit

Kin Leong Kong, Sheila M Willatts, Cedric Prys-Roberts

- The median times from stopping sedation to patients writing their home address were significantly shorter for patients sedated with isoflurane compared with those sedated with midazolam[1]

2

Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device

Peter V. Sackey, MD; Claes-Roland Martling, MD, PhD; Fredrik Granath, PhD; Peter J. Radell, MD, PhD

- Patients sedated with isoflurane emerged from sedation faster than after midazolam[2]
- Time to follow verbal command[2]
  - Isoflurane: 10 ± 8 min
  - Midazolam: 110 ± 130 min

3

Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam—A pilot study*

Peter V. Sackey, MD, PhD; Claes-Roland Martling, MD, PhD; Christine Carlswärd, MD; Örjan Sundin, PhD; Peter J. Radell, MD, PhD

- Sedation of ICU patients with isoflurane may result in fewer delusional memories or hallucinations from the ICU compared with more commonly used intravenous sedation[3]

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1. Kong et al., BMJ 1989. 2. Sackey et al., Crit Care Med 2004.
3. Sackey et al., Crit Care Med 2008.

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Responsiveness after sedation

Fast cognitive recovery

	Midazolam	Isoflurane
Cognitive recovery Median time from stopping sedation to patients being able to write their home address	**275 min**	**58 min**
Range	**75-1440 min**	**20-270 min**

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Kong et al., BMJ 1989.

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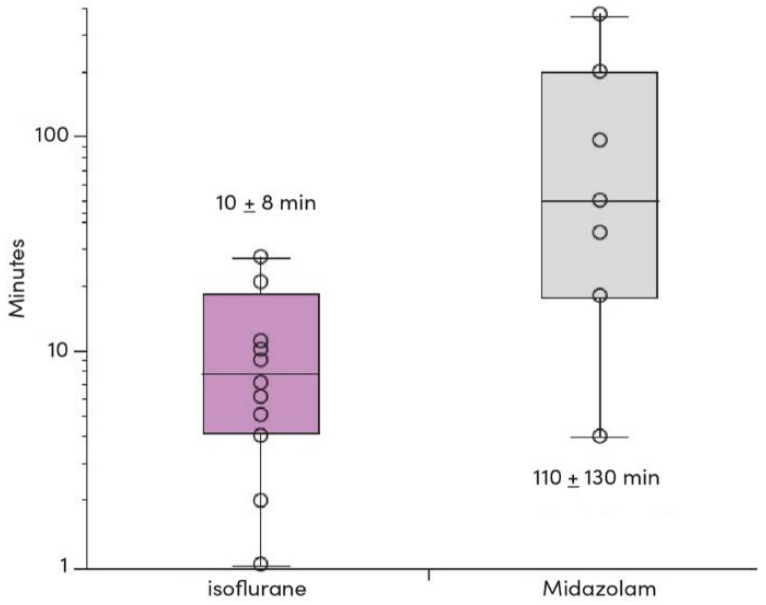
Fast cognitive recovery after 96 hours of sedation

Time to follow verbal command from termination of sedation



- Patients sedated with isoflurane emerged from sedation faster than with midazolam
- Time to follow verbal command
  - Isoflurane: 10 ± 8 min
  - Midazolam: 110 ± 130 min

p=0.003

Sackey et al., Crit Care Med 2004.

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Isoflurane sedation in ICU patients has been associated with a low incidence of hallucinations or delusions

Fast cognitive recovery

Midazolam

5 out of 7

p<0.06

Solely Isoflurane

No cases

0

Sackey et al., Crit Care Med 2008.

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Rapid and predictable emergence from sedation is a clinically valuable feature of a sedative in the ICU

Facilitates **planning** of extubation[1] and **aftercare**, including mobilization[2,3]

Facilitates reliable **neurological evaluation**[4,5] and reduces the need for diagnostic tests[6]

Enables **engagement** with family and staff[2-5]

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1. Meiser et al., Lancet Resp Med 2021. 2. Schweickert et al., Lancet 2009.
3. Green et al., J Multidiscip Healthc 2016. 4. Kong et al., BMJ 1989. 5. Sackey et al., Crit Care Med 2004. 6. Kress et al., N Engl J Med 2000.

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EXPLORATORY STUDIES & FINDINGS

CHAPTER 3

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Preclinical observations in ARDS animal models (inhaled vs IV sedation)

Pulmonary protection

- Reduced levels of inflammatory biomarkers[1-4]
- Reduced levels of markers for epithelial and endothelial injury[1-4]
- Improved arterial oxygenation observed as ratio of oxygen tension to inspired oxygen fraction (PaO2/FiO2)[1-4]

ARDS = Acute Respiratory Distress Syndrome

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1. Voigtsberger et al., Anesthesiology 2009 2. Ferrando et al., Eur J Anaesthesiol 2013. 3. Strosing et al., Anesth Analg 2016. 4. Kellner et al., Anesth Analg 2017.

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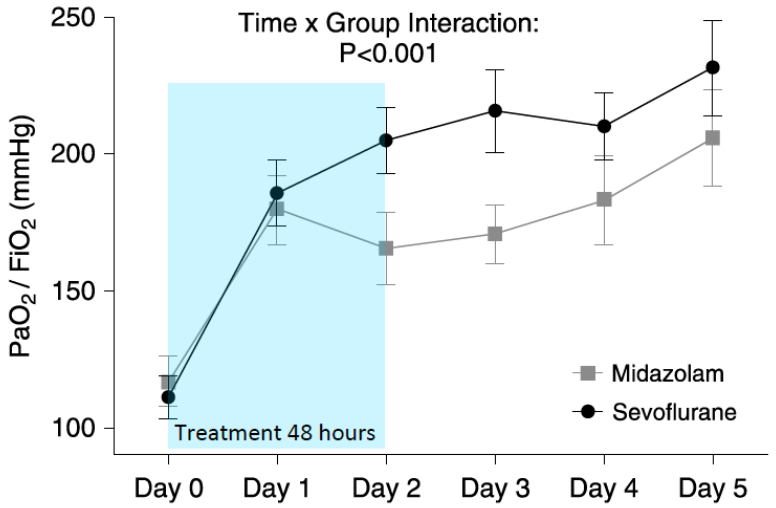
Clinical observations in ARDS patients

Pulmonary protection

Evolution of PaO_2/FiO_2 ratio (mmHg) during the 120-hour observation period (intervention during the first 48 hours)



- On Day 2, PaO_2/FiO_2 ratio was higher in the sevoflurane group than in the midazolam group
- On Day 2, both plasma and alveolar sRAGE levels (an epithelial injury marker) were lower in the sevoflurane group than in the midazolam group

sRAGE=soluble form of the receptor for advanced glycation end-products

Jabaudon et al., Am J Resp Crit Care Med 2017.

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ARDS, cytokines and other indicators - Effects of inhaled anaesthetics

EFFECTS OF INHALED ANAESTHETICS ON ARDS		General findings in ARDS (Sweeney 2016)[1]	Findings in Corona virus infection and ARDS (Huang 2020)[2]	Effects of Inhaled Anaesthetics (isoflurane and/or sevoflurane) vs Intravenous Anaesthetics (controls)				
				Voigtsberger 2009[3] (rat model)	Ferrando 2013[4] (pig model)	Strosing 2016[5] (mouse model)	Kellner 2017[6] (rat model)	Jabaudon 2017[7] (human)
Pro-inflammatory cytokines	TNF-alpha	↑	↑	↓	↓	NA	NA	↓
	IL-1 beta	↑	↑	↓	↓	↓	NA	NS
	IL-6	↑	NA	↓	↓	NA	↓	↓
	IL-8	↑	↑	NA	↓	NA	NA	↓
	IL-10	↑	↑	NA	NA	NA	NS	NA
	MCP-I	↑	↑	↓	NA	NA	NS	NA
	CINC-I	↑	NA	↓	NA	NA	↓	NA
Other markers of lung injury	White blood cell count in alveoli	↑	NA	↓	↓	↓	↓	NA
	Lung fluid permeability/edema	↑	NA	↓	↓	NA	↓	NA
	Alveolar histological disruption	↑	NA	Maintained	NA	Maintained	NA	NA
	S-RAGE	↑	NA	NA	NA	NA	NA	↓
	Oxygenation	↓	↓	↑	↑	↑	↑	↑

ARDS: Acute Respiratory Distress Syndrome; NA: Not assessed; NS: No significant difference

1. Sweeney et al., Lancet 2016. 2. Huang et al., Lancet 2020. 3. Voigtsberger et al. Anesthesiol 2009. 4. Ferrando et al., Eur J Anaesthesiol 2013. 5. Strosing et al., Anesth Analg. 2016. 6. Kellner et al., Anesth Analg. 2017. 7. Jabaudon et al., Am J Resp Crit Care Med 2016. 8. Sackey et al., Crit Care Med. 2004. 9. Mesnil et al., Intensive Care Med. 2011.

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Ongoing clinical studies (ARDS)

Pulmonary protection

The SESAR study[1]

Patient population:
700 intensive care patients with ARDS

Study treatment:
Inhaled sedation with sevoflurane for up to seven days vs intravenous propofol

Primary objective:
Efficacy of inhaled sedation measured as ventilator-free days at day 28, considering death as a competing event

The ISCA study[2]

Patient population:
400 COVID-19-related ARDS patients

Study treatment:
Inhaled sedation (isoflurane or sevoflurane) versus intravenous sedation

Primary objective:
Efficacy of inhaled sedation measured as ventilator-free days at day 28, considering death as a competing event

The SAVE-ICU study[3]

Patient population:
a) Patients with proven or suspected COVID-19, or b) COVID-19 negative patients who have a PaO_2/FiO_2 ratio ≤300 measured with arterial blood gas at least once during the 12 hours prior to enrollment

Study treatment:
Inhaled sedation (isoflurane or sevoflurane) vs standard care (any iv sedation)

Primary objective:
Efficacy of inhaled sedation measured as 1) hospital mortality within 2 years, 2) ventilator-free days within 30 days, 3) ICU-free days within 30 days, 4) participant Quality of Life at 3 and 12 months after discharge.

ARDS = Acute Respiratory Distress Syndrome

ClinTrials.gov Identifiers: 1. NCT04235608. 2. NCT04383730. 3. NCT04415060.

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Reduced bronchospasm

Pulmonary protection

Intensive Care Med (2006) 32:927–933
DOI 10.1007/s00134-006-0163-0

PEDIATRIC BRIEF REPORT

Venkat Shankar
Kevin B. Churchwell
Jayant K. Deshpande

Isoflurane therapy for severe refractory status asthmaticus in children

Isoflurane resulted in:

- An immediate clinical improvement in all 11 children
- An improvement in arterial pH
- A reduction in partial pressure of arterial carbon dioxide ($PaCO_2$) in all 11 patients

Rapid weaning from mechanical ventilation occurred in 10 patients.

Isoflurane for Life-Threatening Bronchospasm: A 15-Year Single-Center Experience

David A Turner MD, David Heitz RRT, Mehrengise K Cooper FRCPH, P Brian Smith MD MPH MHS, John H Arnold MD, and Scot T Bateman MD

Isoflurane led to improvement in pH and pCO_2 in patients with life-threatening bronchospasm:

- Between 4 to 24 hours, there was a statistically significant decrease in PIP (p=0.006)
- FIO_2 decreased within 4 hours of initiation of isoflurane (p=0.001)
- FIO_2 decreased from 4 to 24 hours (p =0.02)

1. Shankar et al., Intensive Care Med 2006. 2. Turner et al., Resp Care 2012.

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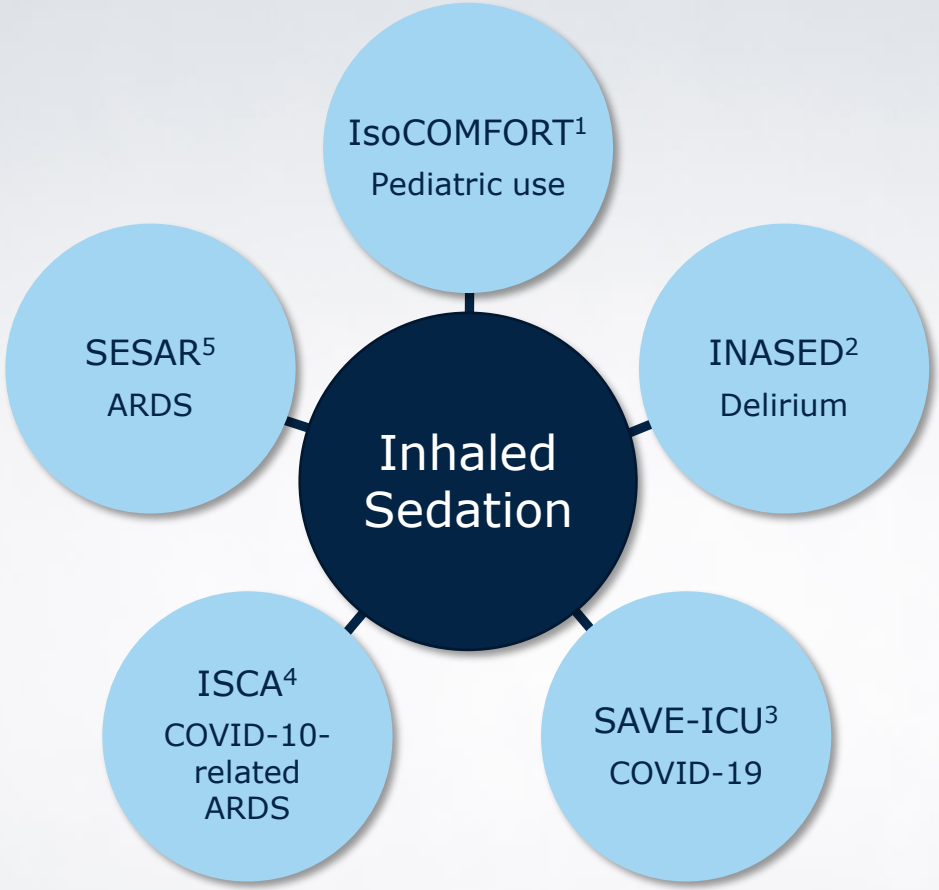
Ongoing clinical studies on Inhaled Sedation in intensive care



ClinicalTrials.gov Identifiers: 1. NCT04684238. 2. NCT04341350. 3. NCT04415060. 4. NCT04383730. 5. NCT04235608.

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SAFETY OF INHALED SEDATION

CHAPTER 4

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Safety of Inhaled Sedation with isoflurane

Adverse reactions to isoflurane are generally dose-dependent extensions of pharmaco-physiologic effects[1]:

- hypotension
- respiratory depression

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1. Sedaconda® SmPC – August 2021. 2. Meiser et al., Lancet Resp Med 2021.

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Important safety information / Precautions

Malignant Hyperthermia (MH)

- Sedation with isoflurane is contraindicated in patients with known or suspected genetic susceptibility to MH.[1]
- MH is a rare genetic disorder (incidence 1/10.000–250.000[2]) where isoflurane sedation may trigger a skeletal muscle hypermetabolic state.

Intracranial Pressure (ICP)

- During sedation with isoflurane, ICP may increase slightly.[1]
- Caution should be taken when administering isoflurane to patients with increased ICP, and ICP must be monitored in such patients.[1]

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1. Sedaconda® SmPC – August 2021. 2. Rosenberg et al., Orphanet J Rare Dis 2015.

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Malignant Hyperthermia (MH)

- In susceptible individuals, isoflurane sedation may trigger a skeletal muscle hypermetabolic state, leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia (MH).
- Known or suspected genetic susceptibility to MH is a contraindication to inhaled sedation.[1]
- Low incidence of MH reactions (1:10,000 - 1:250,000).[2]
- The syndrome includes non-specific features such as:
  - muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and unstable blood pressures
- Treatment of MH includes:
  - discontinuation of triggering agent (isoflurane)
  - IV administration of antidote dantrolene sodium
  - supportive therapy

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1. Sedaconda® SmPC – August 2021. 2. Rosenberg et al., Orphanet J Rare Dis 2015.

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Malignant Hyperthermia and PRIS at a glance

	Malignant Hyperthermia (MH)[1-4]	Propofol-infusion syndrome (PRIS)[5-8]
Triggers	Volatile anaesthetics Succinylcholine	Propofol
Dose-dependent	No	Yes (>4 mg/kg/d; >48h)
Incidence	1:10.000-1:250.000	1,1%
Therapy	Antidote dantrolene Withdrawal of agent, cooling	No antidote Symptomatic
Prevention	Medical history of family MH No use in muscle disease	<4 mg/kg/h, <7 d No use in children <16 y
Mortality	<5%	51%

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1. Larach et al., Anesthesiology 1994. 2. Glahn et al., Brit J Anaesth 2010. 3. Rosenberg et al., Orphanet J Rare Dis 2015. 4. Bandschapp et al., Swiss Med Wkly 2012. 5. Roberts et al., Critical Care 2009. 6. Krajčová et al., Critical Care 2015. 7. Mirrakhimov et al., Crit Care Res Pract 2015. 8. Eziefule et al., Am J Perinatol Rep 2016.

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Low risk of room pollution and exposure of anaesthetic gases to the ICU staff

Scavenging system

FlurAbsorb miminises the exposure to anaesthetic gases during inhaled sedation with Sedaconda ACD

Well below limits

Measured exposure levels for staff are between 0-2 ppm,[1-4] which is well below defined maximum exposure limits

Safe handling

To minimize the risk of exposure, follow the instructions for use for safe handling of the devices.

M/EN/PH/220001 Nov 2021

1. Sackey et al., Crit Care 2004. 2. Gonzalez-Rodriguez et al., Rev Esp Anestesiol Reanim 2014. 3. Pickworth et al., Can J Anaesth 2013. 4. Contreras et al., ESICM Congress abstract 2021.

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ELIGIBLE PATIENTS FOR INHALED SEDATION

CHAPTER 6

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Advantages of Inhaled Sedation

- Reduces the need for multiple intravenous sedatives[1-3]
- Reduces opioid doses, potentially reducing opioid side effects[1-4]
- Facilitates spontaneous breathing[3,4]
- Minimises residual sedation and leads to rapid and predictable wake-up[4] and return of cognitive function[5,6]

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1. Ferriere et al., J Crit Care 2021. 2. Flinspach et al., PLoS One 2021. 3. Meiser et al., Resp Care 2018. 4. Meiser et al., Lancet Resp Med 2021. 5. Sackey et al., Crit Care Med 2004. 6. Kong et al., BMJ 1989.

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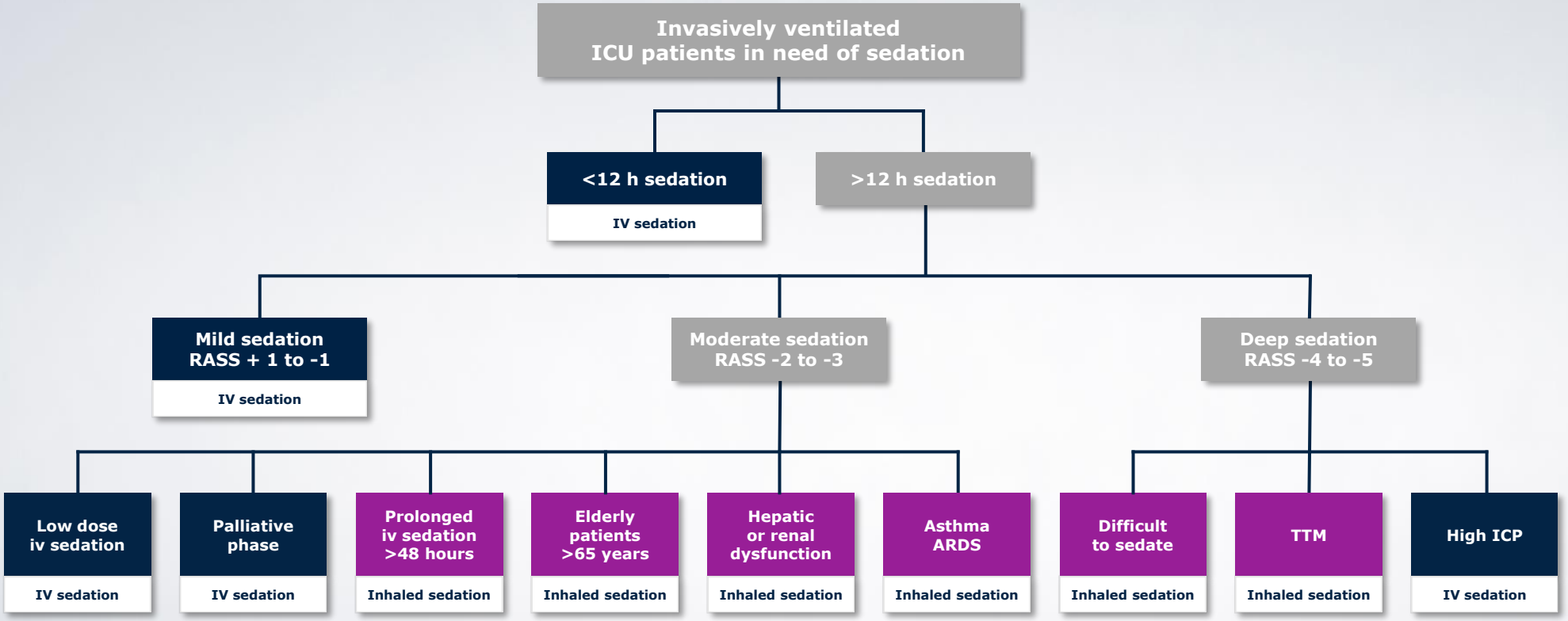
When can inhaled sedation be a good choice for mechanically ventilated ICU patients



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