Sedation in the PICU: various aspects

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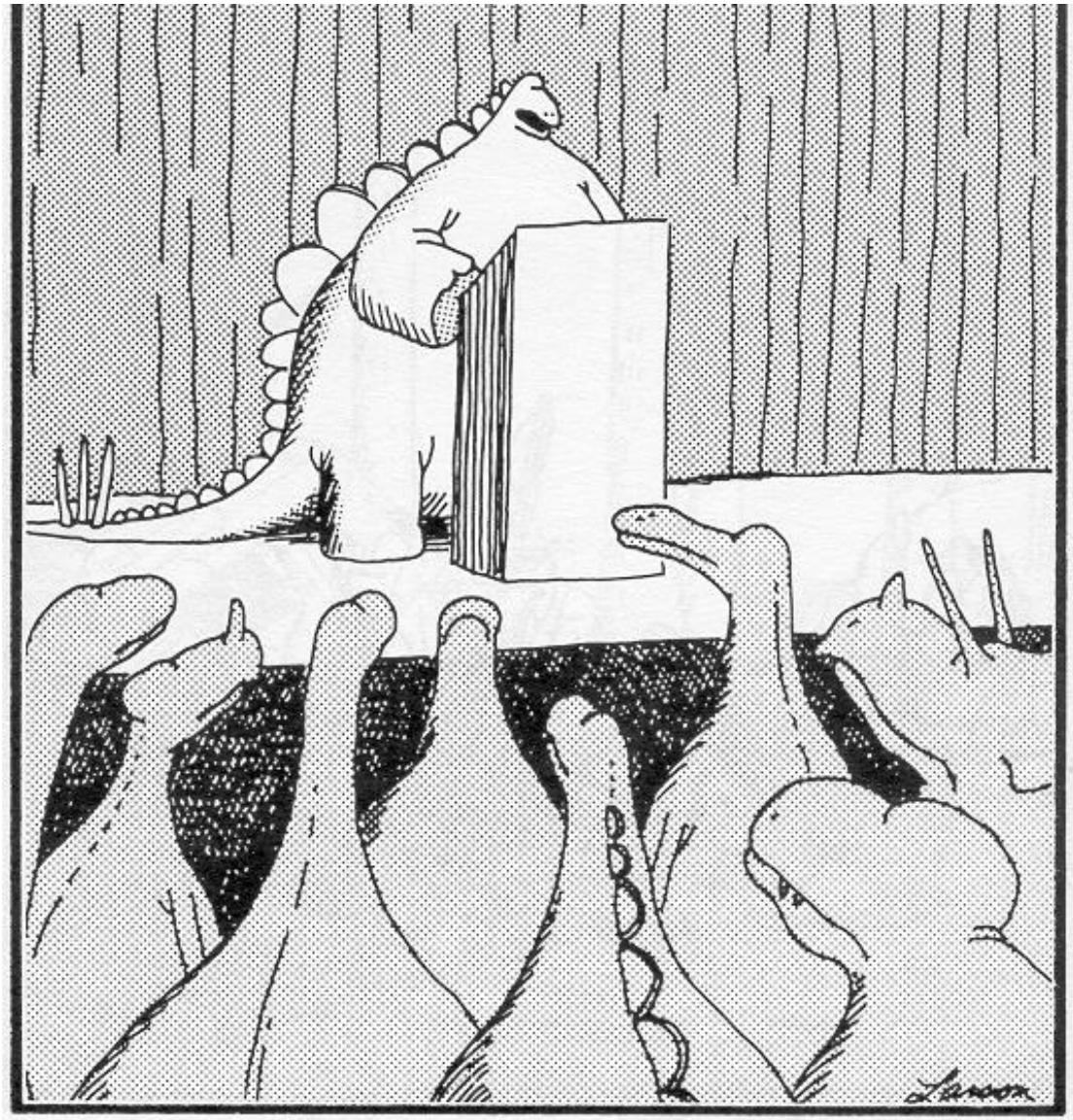
"So! . . . You STILL won't talk, eh?"



"The picture's pretty bleak, gentlemen. ... The world's climates are changing, the mammals are taking over, and we all have a brain about the size of a walnut."

Sedation in PICU Ideal Agent

- **Rapid Onset and Offset**
- **Selective (no effect on CVS, RS, ICP, GI, etc)**
- **No accumulation nor active metabolites**
- **Predictable Elimination**
- **No tolerance or cross-tolerance**
- **No withdrawal symptoms**
- **No toxic effects; immune, metabolic or endocrine**

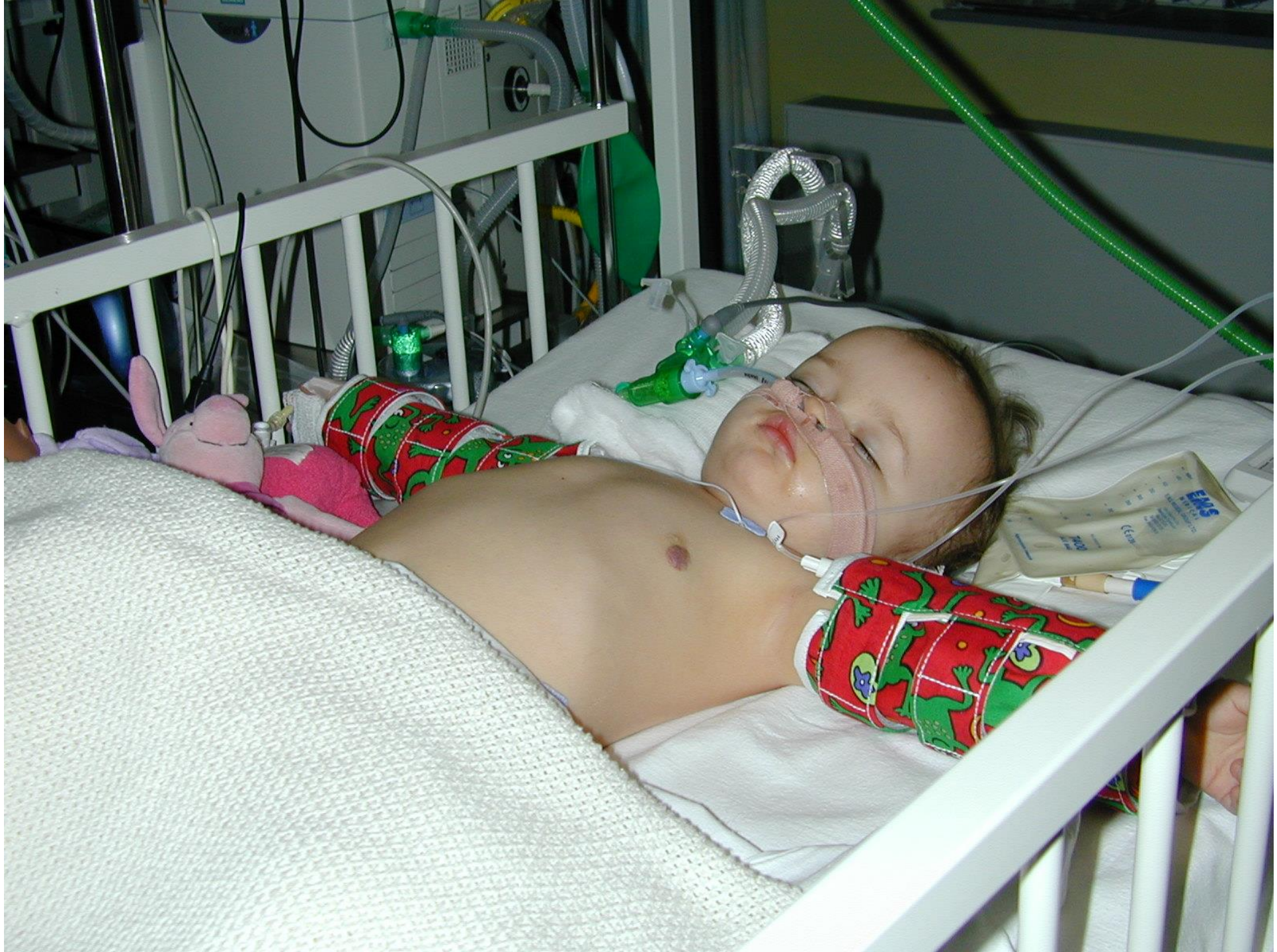
PICU sedation: pro-con

PRO

- Allow adequate PICU care
- Avoid accidental extubation and pulling out lines and catheters
- Reduce patient stress and pain

CON

- Risk for over- and undersedation
- Prolonged time on the ventilator and prolonged PICU stay
- Tolerance, tachyphylaxis
- Withdrawal and abstinence


EMS

International Child Convention

- The ICC is now the law in Sweden
- ”It is never acceptable to hold or restrain a child against its will”
- Not pragmatic
- A balance between a short term discomfort and long-term benefit
- **Important to get parents on aboard**

Pediatric Anesthesia 2007 **17**: 675–683 doi:10.1111/j.1460-9592.2006.02180.x

Current United Kingdom sedation practice in pediatric intensive care

IAN A. JENKINS FRCPE FRCA, STEPHEN D. PLAYFOR DM, CLIFF BEVAN MRCPCH, GERALD DAVIES BA RSCN AND ANDREW R. WOLF MD FRCA

For the Sedation Working Party, Paediatric Intensive Care Society Study Group, UK

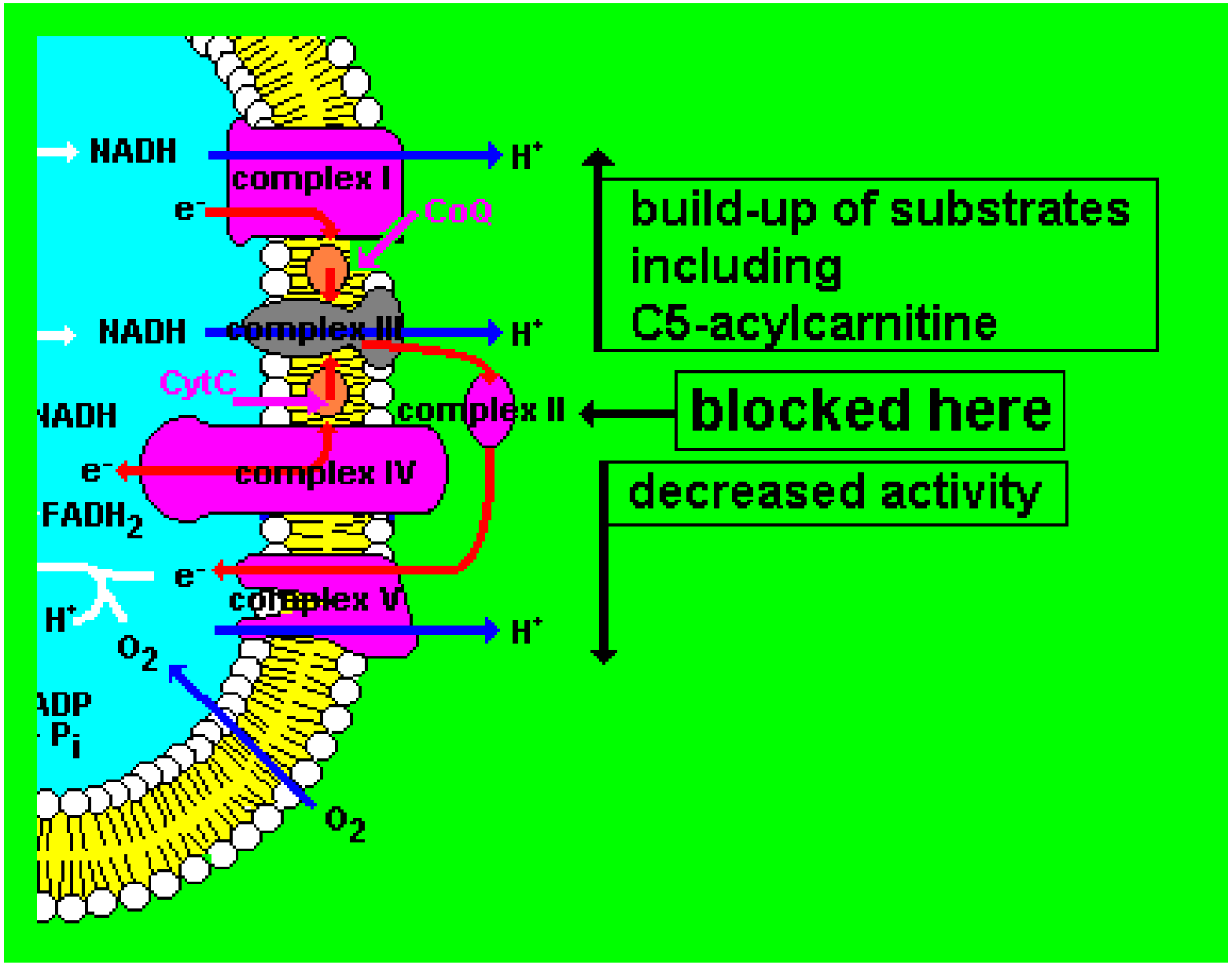
- Prospective, n = 338, 20 UK PICUs
- MO & MDZ most common
- NMB in 30 % of ventilated patients
- Incidence of withdrawal 13 %
- **Physical restraints 7.4 %**
- Propofol 2.6 %, > 4 yrs, < 2 mg/kg/h, no PIS

“Propofol Infusion Syndrome”

1. Sudden onset profound bradycardia
2. Lipaemic plasma
3. Enlarged liver / fatty infiltration at autopsy
4. Metabolic acidosis
5. Muscle damage (Rhabdomyolysis)

Bray RJ. *Paediatr Anaesth* 1998; 8: 491–99

Propofol infusion syndrome (PIS)



Propofol

<u>Unpublished USA Trial</u> 327 children in PICU

- **Propofol at 5.5mg/kg/hr starting dose**
- **3 trial groups:**

1% propofol,	**109 patients with 9 deaths**
2%propofol,	**113 patients with 12 deaths**
Conventional,	**103 patients with 4 deaths**

- **Trial stopped**
- **Propofol withdrawn for use as a sedative in PICU in USA &UK**

COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS in Pharmacovigilance

MEDICINES CONTROL AGENCY

IN THIS ISSUE: Page No.

Internet version: http://www.mca.gov.uk/inspect/monitoring/epadmed/currentproblems/currentproblems.htm

Cerivastatin (Lipobay) withdrawn

Worldwide reporting of rhabdomyolysis

On 8 August 2001, Bayer plc the manufacturer of cerivastatin (Lipobay) voluntarily suspended its marketing and distribution at short notice. There had been concern about the increased risk of rhabdomyolysis associated with its use, particularly when used in combination with one of the fibrates, gemfibrozil (Lopid).

Cerivastatin is a HMG CoA reductase inhibitor, commonly referred to as a statin, indicated for the treatment of hypercholesterolaemia in patients who have not responded adequately to an appropriate diet.

Like all statins, cerivastatin has been associated with a risk of muscle disorders including myopathy and rhabdomyolysis. Since cerivastatin was authorised in the UK 5 reports of rhabdomyolysis have been received through the Yellow Card Scheme.

Spontaneous reports from outside the UK raised concern that the risk of muscle breakdown (rhabdomyolysis) was increased, particularly when cerivastatin is used in combination with gemfibrozil (Lopid).

Europe-wide regulatory action was taken in June 2001 to reduce the risk of rhabdomyolysis, when the concomitant use of cerivastatin and gemfibrozil was contraindicated and the maximum daily dose of cerivastatin was reduced to 0.4 mg. UK health professionals were informed of this action by Bayer plc in June 2001. However, reports of rhabdomyolysis have continued worldwide.

Advice to prescribers:

- Patients who are currently receiving cerivastatin should be changed to alternative treatment when their next prescription is due.
- Any patients who are receiving cerivastatin in combination with gemfibrozil should be recalled for review and alternative lipid lowering treatment should be prescribed.

The CSM has reviewed all the data relevant to the risks and benefits of propofol infusion for sedation in children 16 years of age or younger. On the basis of this the CSM has advised that propofol should be contraindicated in children of 16 years and younger and the product information is therefore being updated.

1. MCA/CSM *Current Problems in Pharmacovigilance* June 1992, No. 34, Vol. 18.

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When is it okay with propofol the PICU

- Various procedures
- Brigde overnight to be extubated in the morning
- ”Very difficult to sedate” cases

- When not okay:
  - As default option
  - Small children, higher doses
  - Beware if circulation is unstable

General issues

- Try to minimize the number of disturbing procedures and painful stimulus and if possible lump them together
- Think about noice (alarms) and light (dim light when possible)
- Try to keep day-night cycle (a place for melatonin??)
- Do not forget IV paracetamol (and IV lidocaine)
- NAVA
- Early mobilization (?)

Clinical features

- **Excessive Crying**
- **Hyperactivity & inattention**
- **Insomnia**
- **Hyperreflexia - tremors - overt seizures**
- **Sweatiness**
- **Poor feeding, vomiting, diarrhoea**
- **Fever**

Sedation in PICU Withdrawal

Incidence:

- **35% in Danish PICU** (Fonsmark L et al, CCM 1999)
- **Particularly if total Midazolam received > 60 mg/kg**

- **17% in UK PICU** (Hughes J et al, Acta Paediatrica, 1994)
- **Symptoms lasted up to 1 week**

Sedation in PICU

Withdrawal

What Drugs cause this?

- **Benzodiazepines**
- **Opioids**
- **Barbiturates**
- **Propofol**

Opioids:

- **Morphine has titratable depressant effect on proliferation of human lymphocytes**
- **Chronic morphine administration is used to render mice immunocompromised**
- **Natural killer-cell toxicity is significantly suppressed after short term morphine in Humans**
- **Specific μ, δ, κ agonists decrease Ig production by human B lymphocytes**

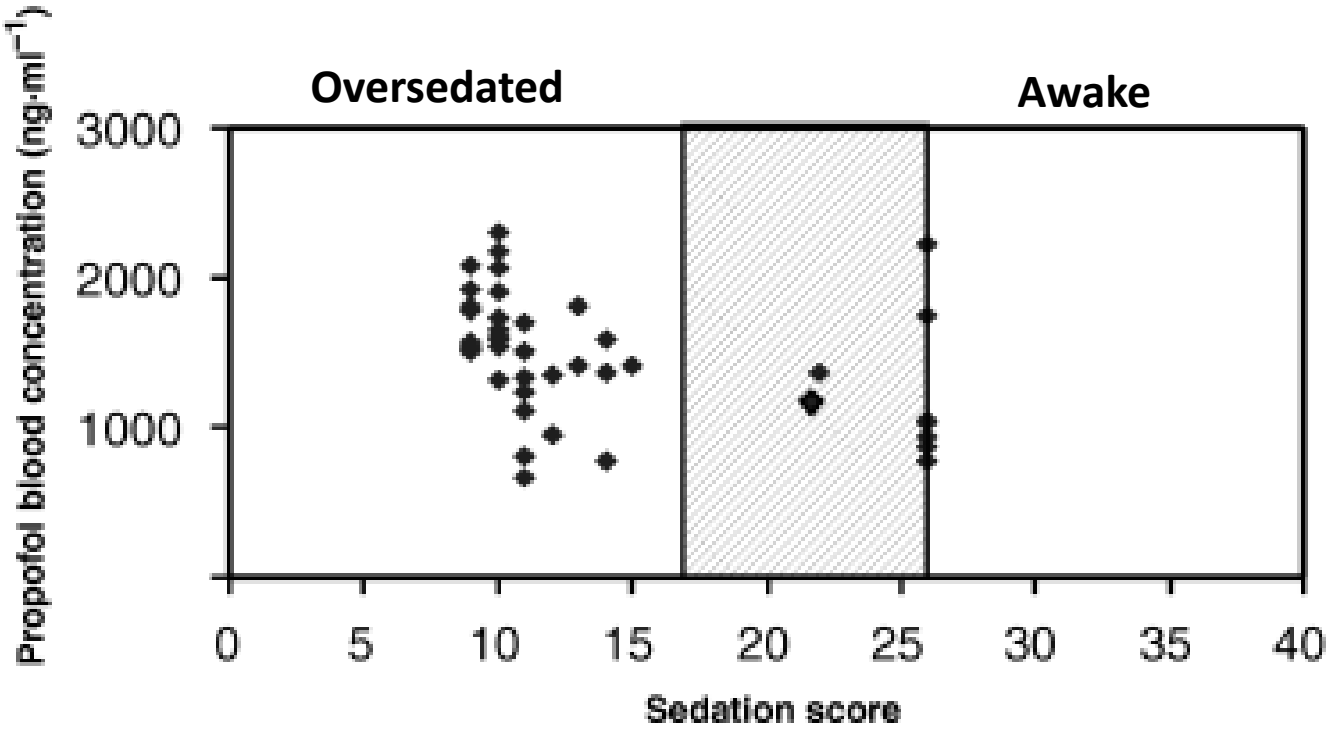
Validated sedation scores

- COMFORT B is the norm
- Somewhat labour intensive
- Difficult to adopt in ICU with only occasional pediatric patients

- Something is certainly better than nothing!

- For pain: FLACC, NRS, others

Electroencephalograph variables, drug concentrations and sedation scores in children emerging from propofol infusion anaesthesia



Pediatric Anesthesia, Volume: 14, Issue: 2, Pages: 143-151, First published: 11 February 2004, DOI: (10.1046/j.1460-9592.2003.01175.x)

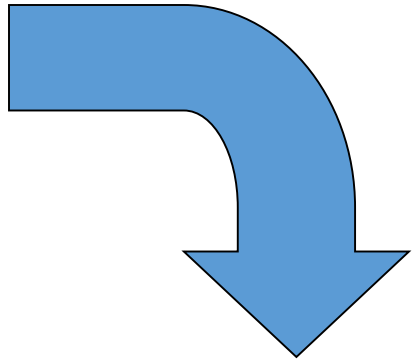
Drug holidays, wake-up tests

- Positive results in adults
- Maybe applicable in teenagers but doutful/not useful in smaller children

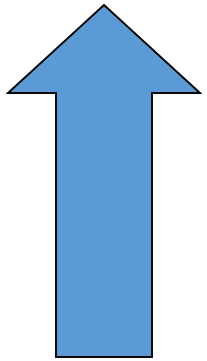
Sedation in PICU

Sparing Strategy- Class Cycling

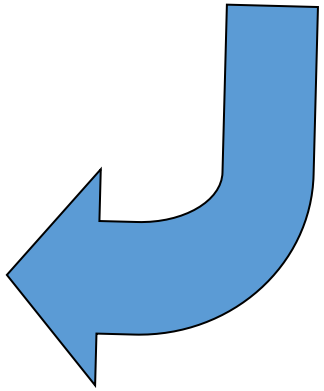
Week 1 Morphine/midazolam
Morphine 10-80 μg/kg/hr
Midazolam 10-150 μg/kg/hr



Week 2 Ketamine/Phenothiazine
Ketamine 10-80 μg/kg/min
Promethazine 500 μg/kg 6hrly prn



Week 3 Clonidine/Chloral
Clonidine 0.1-2.0 μg/kg/hr
Chloral 25-75mg/kg 6hrly prn



Episode Specific Analgesia

- **Regional anaesthesia**
- **Conventional infusions poor tool**
- **Morphine has slow onset**
- **Remifentanil has favourable profile**
- **0.5 mcg/kg/min for 5 min & through episode**

Sedation in PICU

Dealing with Withdrawal

- **More common after > 7 days**
- **Taper drug reduction**
- **Use enteral route if possible: oral methadone, oral diazepam**
- **Combat symptom with appropriate drug class**
- **USE APPROPRIATE WITHDRAWAL SCORE**
  - **Sophia Observation Withdrawal Symptoms-Pediatric Delirium (SOS-PD)**

Isoflurane- the ideal ICU sedative?!

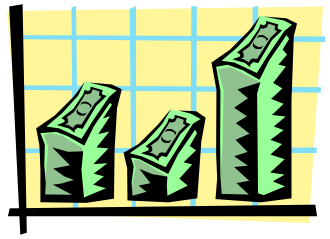
- Easy to titrate to effect, short-acting
- No negative physical or mental consequences for the patient
- Very low degree of metabolism, thus, metabolism ”independent” of organ function
- Organ protective?!

Isoflurane

- Limited physiologic effects: ↓→CO, ↓SVR, ↓BT (dose-dependent), bronchodilatation?
- Minimal uptake and metabolism (0.2%)
- Elimination almost exclusively by exhalation, predictable effect/high degree of control on the level of sedation
- Minimal development of tolerance
- Easy to use for anesthesiologists
- High degree of patient safety (liver transplant)

Isoflurane for ICU sedation - drawbacks

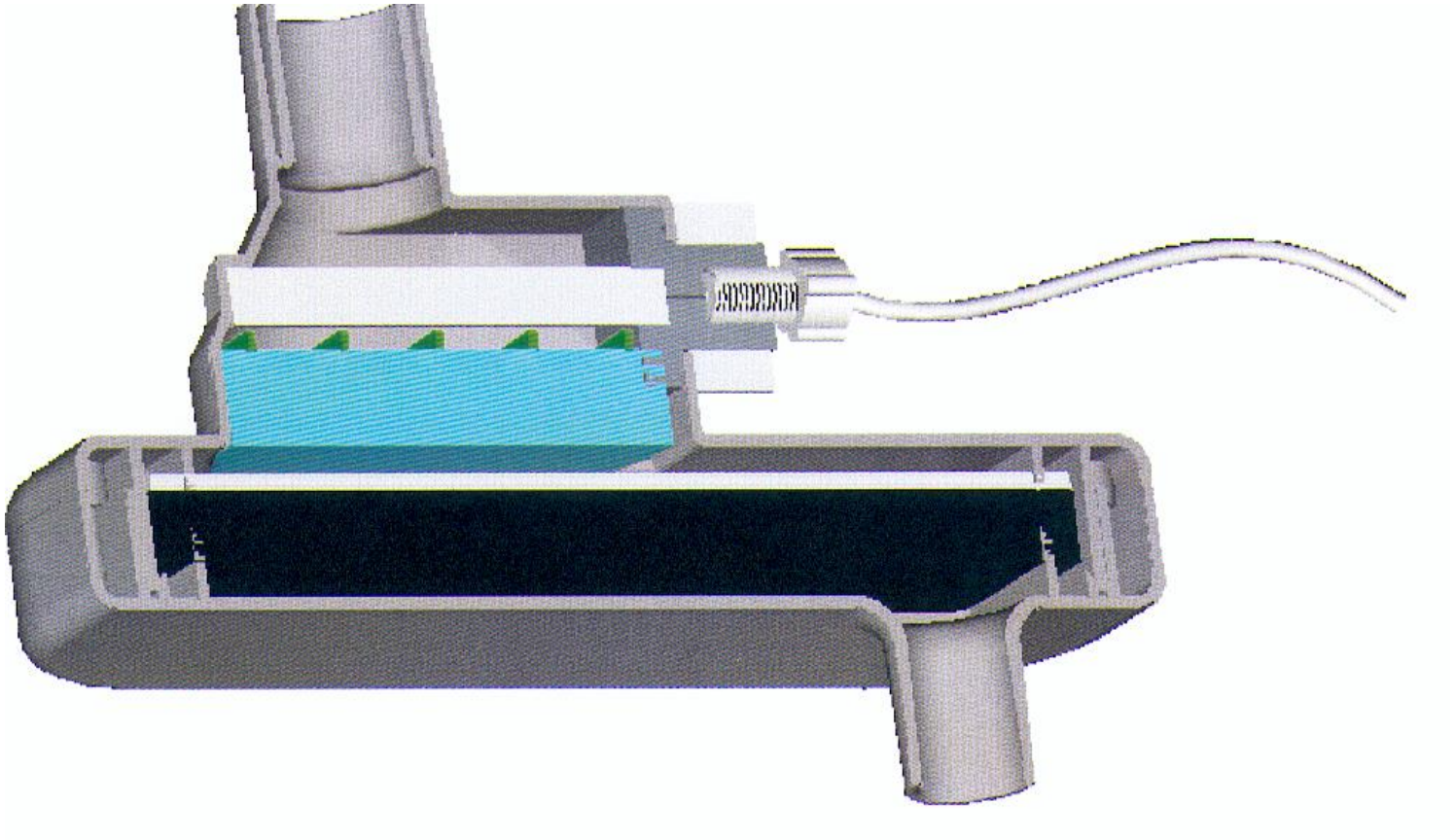
- Normal ICU-ventilators are not built to deliver volatile anesthetics
- New drug for the ICU staff
- Environmental health hazard?
- Requires gas scavenging system
- Following weaning- choreoathetotic movements (spinal effect?)



Anaesthetic Conserving Device

- Modified heat-moisture exchanger
- Contains a filter with active charcoal
- Isoflurane is infused from a syringe-pump into a porous rod
- 90 % of the exhaled isoflurane is ”re-cycled”- very little isoflurane needs to be injected into the system = significant cost savings!

ACD = AnaConDa (Hudson)



Concentration necessary for sedation is only approx. 0.1-0.4 % (1-3 mL/h)

Opioids

- **Morphine**
- Very commonly used
- A number of side effects:
  - Paralytic ileus, obstipation, nausea, vomiting
  - Pruritus
  - Affects ventilatory drive

- Remember to use low dose oral or IV naloxone if needed

Opioids

- **Fentanyl**
- Very common outside Scandinavia
- Context sensitive half-life, accumulation: will prolong effect when stopped/tapered

- **Remifentanil**
  - ”ideal opioid”
  - However, rapid tachyphylaxic and ultra-fast tolerance/hyperalgesia
  - Good choice for short painful procedures

Opioids

- **Methadone**
  - Rapid onset (IV 5-10 minutes)
  - Prolonged half-life
  - Easy to convert morphine and fentanyl to oral methadone
  - Good choice if you need to restrict fluids (avoid continuous morphine infusion)

Alpha-2 adrenoceptor agonists

- Alpha-1/Alpha-2 ratio: Clonidine 1:200 vs. Dexmedetomidine 1:2000
- Half-life: Clonidine 8-12 h vs. Dexmedetomidine 2-3 hours
- Oral bioavaiablilty: Clonidine: 80-100 % vs. Dexmedetomidine: poor and unpredictable
- Nasal administration: Clonidine: does not work vs. Dexmedetomidine works well, dose 2-4 mcg kg-1, onset time 15-30 minutes

- Do produce sedation more similar to sleep
- Do not enhance respiratory depression by opioids

Bensodiazepines

- **Midazolam very widely used**
  - Wide difference in starting doses among PICUs: 10-500 mcg kg-1 h-1
  - Rapid tachyphylaxis
  - Frequent withdrawal
  - Motor manifestations during recovery after long-term used
  - Try to switch to oral diazepam as soon as possible

At the Dog Comedy Film Festival