Sedation in children

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Pharmacological preparation?

Declaration of conflict of interest

Nothing to declare
Reasons for premedication

• Allay anxiety and fear in uncooperative child
• Avoidance of forceful restraint
• Facilitate induction of anaesthesia (iv or inhalational)
• Antisialagogue and anticholinergic

Does it matter?
Reasons for premedication - does it matter?

Children: > 6 yo (n=241)
Elective adeno-tonsillectomy
Anxious vs calm children (m-YPAS)

• Higher self reported pain
• Higher parent reported pain
• Higher emergence delirium (9.7% vs 1.5%)
• Higher postoperative sleep problems
Reasons for premedication - does it matter?

Eating improvement post tonsillectomy

- Low-anxiety group
- High-anxiety group

Day 1
Day 2
Day 3
Day 7
Day 14

Pediatrics 2006;118:651-658
Ideal premedication drug

• Tasteless
• Odourless
• Colourless
• Stable when mixed
• Reliable and reproducible dose dependent anxiolysis
• Routes of administration (PO, PR, IM, intranasal...)

... Does not exist
What is available?

**Commonly used**
- Benzodiazepines
- $\alpha_2$ receptor agonists
- Ketamine
- Opioids

**Older preparations**
- Chloral hydrate and triclofos

**New developments**
- Melatonin and analogues
- Oxytocin (?)
Benzodiazepines

Most commonly used
- Midazolam (0.5-0.7 mg/kg)
- Diazepam (0.3-0.5 mg/kg)
- Temazepam (0.5 mg/kg)
- Lorazepam (0.05 mg/kg)

Gamma-aminobutyric acid receptor complex
Anxiolysis, sedation and amnesia
Benzodiazepines - Midazolam

General Remarks

• Most widely used sedative premedication
• Route and parental preparation
• Plasma concentrations correlate with clinical effect
• Bitter taste, nasal administration very irritant
• Higher doses - delayed emergence and recovery
• Paradoxical excitation
Benzodiazepines - Midazolam

Pharmacokinetics

• Potentially highly variable
• Active metabolite (1OH midazolam)
• Bioavailability and time to peak plasma concentration
  – Oral: 0.27-0.36 and 30-60 min
  – Nasal: 0.55 and 10-15 min
  – Rectal: approx 10 min
• Clearance
• Elimination $t_{1/2}$
Benzodiazepines - Midazolam

Clinical data

Safety: Effects on respiratory function

Children: 3-8 yo (n=18)
Midazolam 0.3 mg/kg 20 min

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre</th>
<th>Post</th>
<th>% change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional residual capacity (mL/kg)</td>
<td>25.0 (1.4)</td>
<td>23.4 (1.9)</td>
<td>-6.5 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung clearance index</td>
<td>6.40 (0.4)</td>
<td>6.89 (0.4)</td>
<td>7.8 (7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>8.64 (1.4)</td>
<td>8.40 (1.5)</td>
<td>-3.0 (4.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>24.6 (3.0)</td>
<td>24.1 (2.9)</td>
<td>-1.7 (5.5)</td>
<td>0.176</td>
</tr>
<tr>
<td>Minute ventilation (mL/kg)</td>
<td>213 (47)</td>
<td>202 (46)</td>
<td>-4.7 (6.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Raw (cm H₂O s/L)</td>
<td>3.38 (0.6)</td>
<td>3.62 (0.6)</td>
<td>7.4 (8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>H (cm H₂O/L)</td>
<td>48.8 (9.7)</td>
<td>52.9 (9.1)</td>
<td>9.2 (8.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are given as mean (sd). Significances as determined with a paired t-test.
Benzodiazepines - Midazolam

Clinical data

Midazolam does not prevent sevoflurane ED

BJA 2010; 104:216
Benzodiazepines - other

- Diazepam
  - Water insoluble
  - Prolonged elimination $t_{1/2}$
  - Peak 60-90 min
- Temazepam
  - Tablet and elixir form
  - Peak 90 min
- Lorazepam
  - Prolonged amnesia
  - Peak 90 min
α₂ receptor agonists

General Remarks
• Inhibit release of NA and sympathetic activity
• Effects via Gαᵢ (AC↓, K⁺/Ca²⁺⁺)
• Binding to receptors in LC and spinal cord

Clinical Effects
• Decrease HR, BP
• Sedation, anxiolysis
• Analgesia
α₂ receptor agonists - clonidine

Pharmacokinetics

• Little known in children
• Erratic absorption
• Peak plasma concentration 30-180 min
• Hepatic biotransformation (p-OH clonidine)
• Renal excretion 50%
α₂ receptor agonists - clonidine

Premedication

• 4 mcg/kg taste, colour & odourless (autistic)
• ‘Steal’ induction
• No effect on
  - Cognitive function or memory
  - Respiratory drive
• Positive effects
  - Reduced anaesthetic requirements & analgesia
  - Less postoperative confusion/ agitation/ ED
α₂ receptor agonists - dexmedetomidine

Pharmacokinetics
• Very limited data
• Bioavailability (16% oral and 82% buccal)
• 8 times more selective than clonidine

Premedication
• 2-4 mcg/kg PO or 1mcg/kg buccal
• Taste, colour & odourless (autistic)
• 30-60 min onset time
\( \alpha_2 \) receptor agonists - Benefits

Clinical data

Clonidine and dexmedetomidine prevent sevoflurane ED
α₂ receptor agonists

Clinical data

Clonidine and dexmedetomidine prevent PONV ???

Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies

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BUT...
The problem with clonidine...
Ketamine

General Remarks

- NMDA receptor antagonist

Volatile anesthetic agents
- Halothane
- Isoflurane
- Sevoflurane

Intravenous anesthetic agents
- Propofol
- Thiopental

\[ Ca^{2+} \]

NMDAR

- PSD95

NO

- L-arginine

GTP \rightarrow cGMP \rightarrow 5'GMP

- cyclicGMP kinases
- Ion channels
- PDE regulation

Anaesth Analg 2007; 105:616
Ketamine

Pharmacokinetics

- The higher the dose the faster the onset
- Large $V_D$, high clearance
- Bioavailability (16% oral to 93% im)

Premedication

- Available in lollipops, elixir and lozenges
- Parental preparation tastes foul
- Onset time <3 min (im) to 30-60 min (PO)
Ketamine

Combination therapy
• Fashionable
• Mixed with benzodiazepines & opioids
• Probably synergistic, no prolonged recovery

Neuronal apoptosis
• Important in animal anaesthesia
• No human clinical equivalent of animal models described
Chloral Hydrate & Triclofos

General remarks

• Bitter taste and gastric irritant
• Standard and established; protocols required
• Serious side effects reported in inadequately monitored patients
Chloral Hydrate & Triclofos

Side effects and profiling

• Prolonged sedation or re-sedation (sick and ex-premature neonates)
• Most effective in children <1 year old; poor >4 years of age
• Good for painless procedures (MRI, CT, echocardiography)

• Doses ranging from 50-100 mg/kg (PO max 2g)
• Onset time is variable:
  faster with higher dose
  top-up doses can be given after 20 minutes
• Offset time is variable

• Monitoring: SpO₂, non-invasive BP
• Avoid: Children with obstructive sleep apnoea

Chalkiadis GA ; 2011
Opioids

General remarks
• Occasionally used
• Sedation less pronounced
• Oral preparations available
• Fentanyl 10-20 mcg/kg (PO); 30-45 min optimum
• PONV, pruritus mild

→ Better alternatives
Barbiturates

General remarks

- Available PR, im, iv routes
- Lipid solubility determines onset and $t_{1/2}$
- Methohexital, tiopental, pentobarbital
- Close monitoring
- Irrelevant in modern practice
Melatonin

**General Remarks**

- Secreted by pineal gland
- Regulating diurnal sleep rhythm
- Frequently used in autistic patients/jet lag
- Taste, colour and odourless, easily mixed
- Dose range 0.1-0.5 mg/kg peak effect approx 60 min
- ? Effectiveness
Melatonin – Jet Lag

Figure 1. Effects of Light and Melatonin on Resetting of the Circadian Clock.

NEJM 2010; 362: 440
Melatonin

Clinical studies
Limited evidence available

Samarkanid (2005)
Children: 2-5 yo (n=105), 15 per group
Minor general surgery
3 doses melatonin/ midazolam/ placebo

EJA 2005; 22: 189
Melatonin

Children: 4-8 yo (n=60), 15 per group
Sedation dental treatment
2 doses melatonin/ midazolam/ placebo

Paed Anaesth 2008; 18: 635
Melatonin

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Melatonin (3 mg)</th>
<th>Melatonin (0.5 mg)</th>
<th>Midazolam (0.75mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hiccup</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Amnesia</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

Children: 4-8 yo (n=60), 15 per group
Sedation dental treatment
2 doses melatonin/ midazolam/ placebo

...melatonin patients asleep shortly after treatment
Melatonin

Other studies

• No additional benefit if added to oral sedation regimen
  - Chloral hydrate or temazepam/ droperidol
  - Average dose 0.3mg/kg (Sury M. BJA 2006; 97: 220)

• Useful for EEG/ MRI ? (Wassmer E. Dev Med Child Neurol 2001;43:735)

• Route relevant (PO vs SL) ? (Naguib M Anesth Analg 2000; 91: 473–479)

• Limited pharmacokinetics data in children

• M1 and M2 receptor agonists (Tasimelteon, Remelteon)
Oxytocin

General remarks

• Nonapeptide secreted from posterior pituitary gland
• Key role in social behaviour
  - Peer recognition
  - Social approach and bonding
  - Emotion recognition
• IV or mucosal application
**Oxytocin**

*Improves emotion recognition for youths with autism spectrum disorders*

Juveniles: 12-19 years (n=16)
Severely autistic
18-24IU oxytocin intranasally cross over
Reading the Mind in the Eyes Test (RMET)

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**Percentage of Correct responses**

- **Total Items**: Placebo - 0.45, Oxytocin - 0.6
- **Easy Items**: Placebo - 0.5, Oxytocin - 0.6
- **Hard Items**: Placebo - 0.35, Oxytocin - 0.6

* Sign indicates significant difference.

*Biol Psychiatry 2010; 67: 692*
Oxytocin

Improves emotion recognition for youths with autism spectrum disorders

Face mask preparation?

Data unlikely from UK centres
Summary

• Anxious patients have worse (surgical) outcomes

• Little published evidence that sedative premedication makes substantial difference

• Single ‘ideal premedication’ agent does not exist

• Selective sedative premedication and combination existing agents adapted to local practice
Further guidelines

Issue date: December 2010

Sedation in children and young people

Sedation for diagnostic and therapeutic procedures in children and young people

NICE clinical guideline 112
Developed by the National Clinical Guideline Centre
Thanks!

Further Reading:
Children of the World Anaesthesia Foundation

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tomkat01@me.com
How to avoid sedation....

• Ingenuity
  – What works:
    – Distraction
    – Re-interpretation
  – What does not work:
    – Threatening
    – Reassurance
    – Bribery