Nitrous oxide/oxygen 50% mixture (EMONO) for procedure pain in children

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Pediatric Pain Unit Trousseau Hospital

- DA = Anesthesiologist + Psychiatrist
  - Director of pediatric pain unit since 1993 (biggest in France...)
  - Dr Tourniaire, Dr Andreu Gallien Dr Gallo
    - Pediatrician, full time
  - Dr Tonelli, Dr Gatbois, Dr Le Goff

- Acute pain service
  - 2 nurses full time

- Chronic pain consultation (700 new patients/year)
  - 85 % migraine and chronic daily headache
  - 2.5 psychologists full time
4 country types relating EMONO use

- High support
  - France, UK, Australia, New Zealand, some US states ...
  - Common use, official guidelines

- Suspicious support
  - sometimes we could use it but we need more data...it is a very old fashioned product, modern pain control need modern tool...

- Opposite
  - \textit{N2O is too dangerous for the planet, humans, it has to be banned}

- Lack of knowledge
  - \textit{N2O can be used out the OT without anesthesiologist ??}
  - \textit{N2O have analgesic properties ??}
Challenge of this course

- Increase knowledge
  - Decrease misconceptions
- Double evidence
  - Review of the literature
  - Clinical benefits for children, parents and health professionals
EMONO used for daily dressing after abscess drainage
Combination with nalbuphine (weak opioid)
https://www.youtube.com/watch?v=zeiSqOUzQnw
A nurse uses EMONO at home
Procedure pain problem

Without paediatric efficient sedation
Strong physical restraint very often needed

➢ 71 % regularly used in Danish ED
  • Sønderskov 2012

➢ 54-28 % for laceration repair
  • McGlone 1998, Babl 2006
Clinical effects

- Anxiolysis, euphoria: *laughing gas*
- Light analgesia (increase pain threshold)
  - EMONO is not able to provide general anaesthesia
  - Conscious sedation
    - the patient can talk, react to environmental stimulations...

- Dissociative state emotional/sensorial
  - Modification of sensory perceptions: visual, auditory...
  - Hypnosis, Ketamine

- Protective airway reflex still functional
Fundamental mechanism

- Opioid release
- Antihyperalgesic properties as N-methyl-D-aspartate receptor
- GABA receptor
- Stimulation of noradrenergic neurons in the brainstem
Historical background

- *Entonox®*(BOC)
- Ambulances, hospital wards, ED, physiotherapy.
- Millions of inhalations in the dental office (adults and children) without any serious adverse effect.
France

- In the late eighties, EMONO used only in the pre-hospital care and in some delivery rooms.

- In 1990, we introduced EMONO in children in hemato oncologic ward: LP, BMA...

- Changes in the inhalation system to improve pediatric use.
  - anesthesia bag
  - Non rebreathing respiratory valve
  - whistle, scented, colored masks
Trousseau Children Hospital Paris

- Academic Hospital
- 250 beds
- ED > 60,000 patients/yr
- > 25 cylinders (1,5 / 3 m³)
  - > 15 different wards
Inhalation number/year

- mean inhalation duration: 10 minutes
  - 2.5% 30 minutes or more.
- 9 euros/inhalation
EMONO Cylinder consumption for 2 weeks in the Hospital Trousseau hematology department
suspicion and doubts regarding the safety of such a method used by non anaesthetists

To face these reactions, we conducted a national survey to assess EMONO use in the pediatric settings in France

1019 inhalations; 31 centers; 2 months

median age : 6.4 (0 -18) years
<table>
<thead>
<tr>
<th>Side effect</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>None</td>
<td>62.8 %</td>
</tr>
<tr>
<td>Euphoria</td>
<td>20.1 %</td>
</tr>
<tr>
<td>Change in visual or auditory perception</td>
<td>7.0 %</td>
</tr>
<tr>
<td>Dream</td>
<td>5.7 %</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3.7 %</td>
</tr>
<tr>
<td>Deep Sedation</td>
<td>2.1 %</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1.5 %</td>
</tr>
<tr>
<td>Nightmare and hallucination</td>
<td>1.2 %</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.9 %</td>
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</tbody>
</table>

- Transient and vanished within 5 minutes
- No serious side effects has been noted.
## Pain assessment

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<tr>
<th></th>
<th>median</th>
<th>Iq</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse (0 - 10)</td>
<td>1</td>
<td>0-3</td>
<td>979</td>
</tr>
<tr>
<td>Child (0 - 100)</td>
<td>9</td>
<td>0-30</td>
<td>649</td>
</tr>
<tr>
<td>Parent (0 - 10)</td>
<td>1</td>
<td>0-3</td>
<td>271</td>
</tr>
</tbody>
</table>
Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children

Gall Lancet 2001

- 7511 inhalations, 18 months, 46 centers
- Inhalation time: 3 - 50 min
  - mean 11 min (SD 6.6)
- Major adverse events in 25 procedures.
- All events resolved within minutes after discontinuation
- No patient needed intervention to maintain the airway

- **Minor** (common side-effects)
  - euphoria, nausea, vomiting, dizziness, paraesthesias
- **Major**
  - oxygen desaturation, airway obstruction, apnoea, bradycardia
  - over-sedation
Prospective safety studies with EMONO
Strong, solid data available

- **1205 EMONO administrations** achieved in 661 patients for dental care; 93% successfull *(Hennequin et al. 2004)*

- **600 patients** (mean age: 5.45) pediatric emergency. *(Kalach et al. Arch Pediatr 2002)*

- **1018 urinary catheterisation** (median age: 4.8 ans) cystography; 70% N2O; nurse administred *(Zier et al. Anesth analg 2007)*

- **1019 administrations** (mean age: 6.4) 31 centers *(Annequin et al. Pediatrics 2000)*
Prospective safety studies with EMONO and N20

- 1221 administrations in 543 patients (1-94 years) uncooperative for dental care (Collado et al. J Clin Psychopharmacol 2006)
- 3310 administrations mostly pediatric (84%), (Giraud et al. J Pharm Clin 2004)
- 7511 administrations 46 french centers included. (Gall et al. Lancet 2001)
- 35828 administrations 191 french centers included (Onody et al. Drug saf 2006)
Characteristics of patients who received a sedative agent for sedation in Melbourne ED Babl 2010

- 67 000 patients over a 4 year period (2004-2008)
- N20 used for 81% (n=1625) of sedation

Safety of high-concentration nitrous Zier 2011

- Nitrous oxide administered at high concentration (up to 70%) for procedural sedation by trained nurses
- Prospective study: 5.5-year period
- 7802 inhalations for 5779 patients (median, 5.0 years)
- No adverse events for 95.7% of cases.
- Nitrous oxide can be safely administered at up to 70% concentration for paediatric procedural sedation, particularly for short (<15 minutes) procedures.
National guidelines for EMONO/EBM criteria

- **appropriate for pain procedures in children who are able to cooperate**

  Scottish Intercollegiate Guideline Network. Safe sedation of children undergoing diagnostic and therapeutic procedures. 2004

- **safe for procedural sedation in children, effective for painful procedures in children**

  Management of procedure-related pain in children and adolescents The Royal Australasian College of Physicians and Paediatrics & Child Health Division 2006)

- **EMONO is the reference product for painful procedures and care in children**

  AFSSAPS 2009
EMONO risks?

- Pollution (greenhouse effect)
- Toxicity neurological
- Fetal, reproduction
Greenhouse Gases and Kyoto Protocol

“aggregate anthropogenic carbon dioxide equivalent emissions“

- carbon dioxide (CO₂)
- methane (CH₄)
- nitrous oxide (N₂O)
- hydrofluorocarbons (HFCs)
- perfluorocarbons (PFCs)
- sulphur hexafluoride


Taken from: Kyoto Protocol, Annex A
Emission of Nitrous Oxide

Total $N_2O$:
4.9% of total emissions

- **energy**
- **chemical industry**
- **medicine** (about 1%)
- **solvent- and other product use**
- **agriculture**

**medical $N_2O$**
< 0.1% of total emissions

Data from Germany: Ministry of Environmental Protection
Neurological toxicity and Vitamin B12 deficiency (chronic exposure or risk patient)

- Chronic, sustained inhalation (G.A, addiction)
- Inhibition of methionine synthetase required for myelin phospholipids
- Vitamin B12 deficiency produce spinal dorsal cord degeneration.

Clinical symptoms

- myelopathy, peripheral axonal neuropathy, or both, with combinations of paraesthesia, gait ataxia, sphincter disturbance and pyramidal weakness

- Reversible after 3 days substitutive treatment.
Occupational exposure

- Slight decrease fertility among 19/7000 dental assistant (>5 h/week) Rowland Nejm 1992
- No effect (spont abortion) among 4000 swedish midwives Ahlborg Occ Env Med 1996
- No significant effects on healthcare personnel, associated with the occasional intermittent use of EMONO has been observed. AFSSAPS 2009
- "limited data to clearly substantiate concerns about the reproductive toxicity of occupational exposure to N2O at levels below the currently recommended and accepted guidelines" Tobias JD Pediatr Emerg Care 2013
Simple ways to limit exposure

- Scavenging systems must be available if EMONO still used in the same place
- Moving tank + space ventilation
- Collecting pipe through the window

Extractor machines available
Nitrous oxide labor analgesia is safe for the mother, fetus, and neonate and can be made safe for caregivers.

It is simple to administer, does not interfere with the release and function of endogenous oxytocin, and has no adverse effects on the normal physiology and progress of labor.
Teratogenicity

- *N2O teratogenicity demonstrated in rats can not be extrapolated to humans* Fujinaga 2001, Rosen 2002

- registry study of 5405 cases
  - frequency of congenital malformations, not higher among women who received nitrous oxide at the time of surgical anesthesia during the first trimester of pregnancy Mazze R. J Obstet Gynecol 1989
High homocysteine level

- Adult (general anesthesia)
  - Oxidation of vitamin B12 impairs conversion of homocysteine to methionine *Myles PS BJA 2008*
  - Increased incidence of adverse postoperative cardiovascular events?

- Exposure to < 2 h nitrous oxide is not associated with increase in postoperative plasma total homocysteine concentrations *Pichardo, D Anesthesiology. 2012*
Controversy: N2O and General Anesthesia cardiovascular complications

- **ENIGMA study**: 2050 patients randomly assigned [Myles PS. Anesthesiology 2007;](#)
  - Increase (non-significant trend) cardiovascular complications

- **21,500 matched patients**, noncardiac surgery [Cleveland Clinic Turan A Anesthesia Analgesia May 2013](#)
  - 33% decreased odds of 30-day mortality
  - 17% decreased odds of in-hospital morbidity and mortality
  - 41% decreased odds of pulmonary morbidity

➢ *Overall, the findings of Leslie for now, are reassuring* [McKay RE Anesthesia Analgesia May 2013](#)
This Wonder-Working Gas
Kirk Hogan, MD, JD* and Paul S. Myles, MD, MPH†

Comparing Apples to Oranges: Just Say No to N₂O?
Thomas R. Vetter, MD, MPH, and Gerald McGwin, Jr., MS, PhD

Nitrous Oxide and Cardiovascular Outcome: Perspective from the POISE Trial
Rachel Eshima McKay, MD
Post hoc subanalysis

1489 (29%) N20 of 5133 patients

No increase of myocardial infarction, stroke, death, and clinically significant hypotension.
Controversy: N2O and General Anesthesia

- DNA damage (70% N2O for colorectal surgery) Chen Y. Anesthesiology 2013
  Transient effect, clinical validity? Hogan K. Anesthesiology 2013

- Postsurgical pain
  - nitrous oxide administration is associated with a reduced risk of chronic postsurgical pain Chan MT. Pain 2011
French official guidelines for pediatric sedation 2009

PRISE EN CHARGE MEDICAMENTEUSE DE LA DOULEUR AIGUË ET CHRONIQUE CHEZ L’ENFANT

Partie 1 : Prise en charge de la douleur en milieu hospitalier et situations particulières en ville
French guidelines (EMONO)

✓ EMONO is the reference product for painful procedures and care in children as it possesses a series of original properties:

✓ speed and reversibility of action
✓ analgesic/anxiolytic effect
✓ good risk/benefit profile (Grade A)
French guidelines (EMONO)

✓ It does not cover all painful procedures and care.
✓ Depending on the indications, the child's age and the experience of the healthcare providers
✓ 100 - 70% success is observed.
✓ Children < 2 years have less pronounced effects.
- EMONO should be administered by specifically trained medical or paramedical staff

- A prolonged administration at a given location, a gas scavenging system must be available.

- Regular airing of the room, combined with the use of a mobile cylinder allowing administration at the patient’s bedside, or in a different room, represent simple measures that can be used to control problems associated with occupational exposure to N2O.
When these precautions are taken, no significant effects on healthcare personnel, associated with the occasional intermittent use of EMONO has been observed.
Summary

- EMONO is not a general anesthesia
- Slight disadvantages
  - not efficient in all patients
    - 70 - 100 % success rate
  - failures must be anticipated to switch to deeper technique.
  - best results are obtained in children aged over 2 - 3 years
  - Require time to prepare child and mask acceptance
Summary

- **Major advantages**
  - **Very high safety level**
    - no serious adverse effect after million inhalations
  - Efficient after 3 minutes inhalation
  - Fasting unnecessary
  - Trained nurses are able to administer this analgesic technique without medical presence.
Cross the barriers

- Strong safety efficiency data
- Excessive misconceptions
  - adverse effects, side effects, toxicity, pollution, overestimated
- Patient centred medicine (child need), ethical pow
- This method is still underused, and it should be readily available in each emergency and paediatric (adult ...) department.
TRAINING VIDEO (FRENCH)

http://www.youtube.com/watch?v=pL3Tw_jSAus
Complete references
Dr Annequin presentation ISPP 2013
Nitrous Oxide mixture 50%

annequindaniel@yahoo.fr

Complete references
http://bit.ly/12Q7vhS

Slides
La douleur de l'enfant

→ Recommandations Afssaps 2009

Vidéos disponibles

Faut-il vraiment continuer à évaluer la douleur?
Dr Élisabeth Fournier-Charrière,
Dr Barbara Tormina, Bénédicte Lombart
Communication aux 19e journées
"La douleur de l'enfant. Quelles réponses ?"
(décembre 2012)

Journées PédiaDol

2-4 décembre 2013 :
les 20e journées !
→ Ateliers de formation 2 & 4/12
→ Journée plénière 3/12
→ Inscriptions en ligne

Lu pour vous

→ Le best-of de la littérature 2011-2012

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Lettres d’information

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