What is the deal with nitrous?

Eric Deutsch MD
Overview of Topics

• History of Nitrous Oxide
• Pharmacodynamics
• Pharmacokinetics
• How labor nitrous is packaged and administered
• Adverse Drug Reactions of Nitrous
• Environmental concerns
• Evidence of efficacy?
• Patient selection
• How SLH started their L&D nitrous service
Disclosure

• No corporate, financial contracts, or investments to disclose
Introduction

• “Labor is a complex and highly individualized process; not every woman wants or needs analgesic intervention for delivery”


Anesthesiologists from Harvard’s Brigham and Woman’s Hospital
The perfect labor analgesic...

1. Would eliminate all pain (nociceptors)
2. Is noninvasive
3. Would not block sensation of body/limb movement and position (proprioception)
4. Would permit ambulation (not block motor function)
5. Would not alter cognition
6. Could be easily and quickly converted to a surgical anesthetic (national c-section rate is 32.8%)*
7. Is safe and has no complications or side effects
8. Can be quickly implemented and quickly discontinued by non-experts
9. Is inexpensive

Chronic pain syndromes and labor pain

McGill questionnaire pain scores (PRI)

Pain after accidents

Causalgia

Nulliparas (no prepared childbirth training)

Nulliparas (prepared childbirth training)

Multiparas (trained and untrained)

Chronic back pain

Cancer pain (nonterminal)

Phantom limb pain

Postherpetic neuralgia

Toothache

Arthritis

50

40

30

20

10

Digit amputation

Bruise

Fracture

Cut

Laceration

Sprain

Medical Interventions

IF YOU GIVE A MOUSE A COOKIE

There was an old lady who swallowed a fly.

Laura Joffe Numeroff
Illustrated by Felicia Bond

Simms Taback
Nitrous Oxide (N₂O)

- Inhaled N₂O was introduced in 1881 to provide pain relief during labor
- Its routine use for labor analgesia began after introduction of an apparatus for self administration in 1934
- Used by 60% of laboring women in the UK
- Used ~ 50% of laboring women in Australia, Finland and Canada.
- In the US, there appear to be a few institutions where it is routinely available (UW, UCSF, Vanderbilt, St. Joseph’s in Lewiston Idaho, and St. Luke’s Hospital)
Nitrous Oxide (N₂O) • Premixed 50:50 N₂O:O₂ • Connected through a demand valve which opens with sufficient negative inspiratory pressure • Very modest reduction in labor pain • Interestingly, some women who report no benefit request to continue its use • Safe for fetus (APGAR & cord gases) • occupational exposure risk (Inactivation of methionine synthase)

Pharmacodynamics & Pharmacokinetics

• Greatest relief when inhaled ~ 30 seconds prior to contraction results in highest serum peak concentrations

• MOA
  o Triggers endogenous opioid release
  o N-methyl-d-aspartate receptor inhibition reduces hyperalgesia (similar to ketamine)
  o Anxiolysis mediated by central gamma-aminobutyric acid receptors may enhance the euphoric properties (similar to benzodiazepines and ETOH)
  o Stimulatory activity at dopaminergic, and α₂ adrenergic receptors

• Nitrous oxide is eliminated unchanged from the body

Nitronox™

Porter Instruments, Hatfield, PA  ~$5,500
ENTONOX™

Not available in the United States
Pin index safety system
Medical gas line Safety Systems

Wall connections

Chametron

Ohmeda

Oxaquip

Puritan-Bennett

Schrader

DISS = Diameter Index Safety System
Oxygen vs Nitrous e-cylinder

Note the red indicator on each tank gauge.
“If it cannot be measured, it cannot be studied”

- A common academic saying
Comparison of N₂O efficacy with other analgesic methods

• NOTE - Studies that evaluate the efficacy of techniques used for labor analgesia are difficult to design
• There are numerous studies, but most are done prior to 2000
• Summary – Nitrous is approximately as efficacious as opioids

<table>
<thead>
<tr>
<th>Analgesic method</th>
<th>VAPS reduction (scale 0-10)</th>
<th>Sedation (scale 0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural</td>
<td>-5</td>
<td>0</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>-1.5</td>
<td>2</td>
</tr>
<tr>
<td>Nitrous</td>
<td>-0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

# Epidural vs Nitrous

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Nitrous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dense/significant pain relief</td>
<td>Dense/significant pain relief</td>
<td>Variable and modest pain reduction</td>
</tr>
<tr>
<td>No effect on anxiety*</td>
<td>No effect on anxiety*</td>
<td>Significant anxiolysis</td>
</tr>
<tr>
<td>Invasive</td>
<td>Invasive</td>
<td>Noninvasive</td>
</tr>
<tr>
<td>expert personnel required</td>
<td>expert personnel required</td>
<td>No special skills required</td>
</tr>
<tr>
<td>Monitoring required</td>
<td>Monitoring required</td>
<td>No monitoring required</td>
</tr>
<tr>
<td>Serious side effects are uncommon</td>
<td>Serious side effects are uncommon</td>
<td>No serious side effects when used in labor</td>
</tr>
<tr>
<td>Restricted to bed</td>
<td>Restricted to bed</td>
<td>Unrestricted ambulation</td>
</tr>
<tr>
<td>Needs IV access and urinary catheter</td>
<td>Needs IV access and urinary catheter</td>
<td>Does not require either</td>
</tr>
<tr>
<td>Able to convert to surgical anesthesia</td>
<td>Able to convert to surgical anesthesia</td>
<td>Not possible as MAC of 104%</td>
</tr>
</tbody>
</table>

* Debated

Most common ADR with Nitrous Oxide:

- Mild respiratory depression/hypoxia (debated)
- Drowsiness
- Vertigo
- Nausea (debated)
- No effects on uterine activity
- No increase in maternal nausea or vomiting during labor.


Candidates for Nitrous...

- Parturients who are not NAA candidates
- Parturients who are rapidly progressing
- Parturients who want to ambulate, avoid bladder catheterization, or avoid IV access.
- Vaginal repairs
- Retained placental products
Non-Candidates...

- Parturients with “at risk*” fetuses
- Persons in the labor room who are 1st trimester or wish to become pregnant (nurses and visitors).

* Non-reassuring fetal strips or parturients requiring oxygen
Nitrous Cost

• St. Joseph in Lewiston charges flat fee of $107

• Labor epidural cost is dynamic. Approximately $1000 to $1400 at SLH

• Cost roughly equates to efficacy and complexity of management.
Occupational exposure limits

OSHA* Not currently regulated
NIOSH** 25 ppm time weighted average for duration of use (for exposure to “waste” gas.)
ACGIH*** 50 ppm time weighted average for an 8-hr use

* Occupational Safety and Health Administration
** National Institute for Occupational Safety and Health
*** American Conference of Governmental Industrial Hygienists
Spontaneous Abortions and Scavenging

• Spontaneous abortions in rats at ≥ 1000 ppm
• Vertebral and rib defects in rats after days of exposure to >45% concentration of nitrous
• NIOSH reports concentration of ≥ 1000 ppm in nonscavenged settings

• “Scavenging equipment can make large differences in exposure levels at moderate cost and appears to be important in protecting the reproductive health of women who work with nitrous oxide”
• There have been multiple epidemiological studies that both support and refute a cause an effect relationship
More elephants...

- There is accumulating evidence that anesthetic agents result in neurodegeneration of the developing brain (rat and primate).

- However, Nitrous oxide at subanesthetic concentrations, reportedly triggers little or no neuroapoptosis

- Ma D, Williamson P et al. Xenon mitigates isofluraneinduced neuronal apoptosis in the developing rodent brain. *Anesthesiology* 2007;106:746–53
Occupational exposure

Proposed SAB mechanism
Implementation models

• Anesthesia Model
  - Anesthesia is comfortable with Nitrous and gas blenders.
  - Unfortunately, there is no “code” for nitrous administration.

• Nursing/Hospital Model
  - Analgesic modality that is controlled by L&D
  - Nitrous has a better safety profile than IV or IM narcotics
  - Nitrous is commonly used for dental procedures without monitoring.
  - There are billing and implementation models already in place
How Nitrous was implemented at SLH
SLH Nitrous Policy
Other pharmacological options

- Narcotics (Ex; Remifentanil PCA)
- Ketamine
- Dexmedetomidine

All three may be moderately more effective than inhaled nitrous, but have more ADR’s and more complicated setup.
Summary

- Nitrous oxide, although providing only a modest reduction of pain, gives laboring women an inexpensive, non-invasive, and easily implemented pharmacological option for labor analgesia with essentially no serious adverse reactions for mother or baby.

- Nitrous has an 80 year safety record in labor decks around the world.
Good Review Reading

• Quarnstrom F. Nitrous oxide analgesia. What is a safe level of exposure for the dental staff? Dent Today. 2002 Apr;21(4):104-9
Thank you!

Dogbert, Career Counselor: According to your occupational preference test, you like to remove vital organs from helpless people.

That narrows the career choices to doctor or serial killer. Do you get along with other people?

Other people are insignificant insects.

We'll have to go to a tie-breaker question.
Questions? Comments?