MTHFR: Impact of Nitrous Oxide

Presenter:
Benjamin Lynch, ND

International Academy of Biological Dentistry and Medicine Conference
Las Vegas, NV

“Clinicians will be central to helping consumer-patients use genomic information to make health decisions.” – NEJM

(c) 2014: Benjamin Lynch, ND
Disclaimer & Disclosures

The information presented here is for informational and educational purposes only. Docere, Inc and Benjamin Lynch will not be liable for any direct, indirect, consequential, special, exemplary, or other damages arising from the use or misuse of any materials or information published.

President and CEO of SeekingHealth.com, SeekingHealth.org and founder of MTHFR.Net
Genetic and Epigenetic Contributions to Human Nutrition and Health: Managing Genome–Diet Interactions

PATRICK J. STOVER, PhD; MARIE A. CAUDILL, PhD, RD

ABSTRACT
The Institute of Medicine recently convened a workshop to review the state of the various domains of nutritional genomics research and policy and to provide guidance for further development and translation of this knowledge into nutrition practice and policy. Nutritional genomics holds the promise to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better targeted public health nutrition interventions (including micronutrient fortification and supplementation) that maximize benefit and minimize adverse outcomes within genetically diverse human populations. As the field of nutritional genomics matures, which will include filling fundamental gaps in knowledge of nutrient–genome interactions in health and disease and demonstrating the potential benefits of customizing nutrition prescriptions based on genetics, registered dietitians will be faced with the opportunity of making genetically driven dietary recommendations aimed at improving human health.


Public health nutrition continues to be challenged by increasing expectations from the food supply on one hand, and fundamental gaps in nutrition knowledge on the other, which can constrain the development and implementation of nutrition and food policy (1). Current demands on the food supply are no longer limited to ensuring general safety and preventing micronutrient deficiencies. Increasingly, there is interest in engineering medicinal qualities into the food supply to enable diets that promote health and “nurture” a sense of well-being that transcends the mere absence of disease by improving biological functions and even increasing life spans.

Unquestionably, nutrition is one of the primary environmental exposures that determines health. Common human chronic diseases, including type 2 diabetes, metabolic syndrome, cardiovascular and neurological disease, and many cancers are initiated and/or accelerated by nutrient/food exposures. However, it is also recognized that chronic diseases are complex in their etiology and include a substantial genetic component; individuals respond differently to foods and even individual nutrients. Investigation in this new field of nutrition research, often referred to as nutritional genomics, focuses on deciphering the biological mechanisms that underlie both the acute and persistent genome–nutrient interactions that influence health.

Nutritional genomics, while centered on the biology of individuals, distinguishes itself from other “omics” fields by its unique focus on disease prevention and healthy aging through the manipulation of gene–diet interactions. Nutritional genomics promises to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better...
Methylation

Donating Methyl Groups

$\text{CH}_3$
Methylation is the process of controlled transfer of a methyl group (CH$_3$) onto amino acids, proteins, enzymes, and DNA in every cell and tissue of the body . . .

This process is one of the essential metabolic functions of the body and is catalyzed by a variety of enzymes.
Tyrosine methylation process:

- **Uracil** (RNA) is converted to **Thymine** (methyl-Uracil) by the **TYMS enzyme**.

  - Methyl group from 5,10 MTHF is added to **Uracil** to form **Thymine** (DNA).
Methylation

Functions of Methylation (some):
- Gene regulation: turn on/off genes via SAMe
- Biotransformation: glutathione production
- DNA base formation: uracil → thymine
- Neurotransmission
- Cell membrane: phosphatidylcholine and DHA to membranes
- Adenosine as metabolic fuel regulator (acetyl CoA vs lactate)
- Cell protection: NFkB expression to reduce TNF cytotoxicity

Methylation

Methyl Donors – donate a methyl group - CH$_3$

- Methylcobalamin (B12)
- Methylfolate (Folate)
- Methionine
- Choline
- Glycine
- TMG
- DMG
“SAM, a remarkably versatile molecule, is said to be second, only to ATP, in the number of enzymes that require it.”
FIGURE 1. Major reactions involved in transmethylation flux and methylneogenesis. The total transmethylation flux is equivalent to the total flux occurring through reactions that convert S-adenosylmethionine to S-adenosylhomocysteine. The 3 S-adenosylmethionine-dependent reactions thought to contribute quantitatively most to this flux are methylation of guanidinoacetate by guanidinoacetate methyltransferase (GAMT) to form creatine; methylation of phosphatidylethanolamine by phosphatidylethanolamine methyltransferase (PEMT) to form phosphatidylcholine; and methylation of glycine by glycine N-methyltransferase (GNMT) to form sarcosine (N-methylglycine). A large number of additional S-adenosylmethionine-dependent methyltransferases also occur in mammals [see Katz et al (3)], but their collective quantitative contribution to transmethylation flux may be small compared with those mentioned above. The final steps in methylneogenesis are the reduction of a methylene group of 5,10-methylenetetrahydrofolate (methylene-THF) by methylenetetrahydrofolate reductase (MTHFR) to form 5-methyltetrahydrofolate (methyl-THF), followed by transfer by methionine synthase of the newly formed methyl moiety to homocysteine, forming methionine and tetrahydrofolate (THF). Sarcosine is formed not only by GNMT, but also by oxidation of choline to betaine, formation of dimethylglycine by betaine homocysteine methyltransferase (BHMT), and oxidation of dimethylglycine to sarcosine. Sarcosine is oxidized by sarcosine dehydrogenase (SDH). During the reaction, glycine is produced, and a 1-carbon unit is transferred to THF, forming methylene-THF. MAT, methionine adenosyltransferase; CBS, cystathionine β-synthase; CGL, cystathionine γ-lyase; SAHH, S-adenosylhomocysteine hydrolase.
MTHFR snp can reduce one type of cancer risk. Which one?
Nitrous Oxide

Bad?
Nitrous oxide is employed in dentistry for the primary purpose of reducing anxiety in the dental patient.

It is estimated that 20 to 40 million adults in America avoid dental treatment because of fear.
“The effect is well known among anesthetists that nitrous oxide irreversibly inactivates cob(I)alamin, the active form of vitamin B12 essential for methionine-synthase activity in the brain and converts it to cob(II)alamin.”
Nitrous Oxide Effect
Table 2. Summary of current papers available which study the effects of N\textsubscript{2}O alone, including case studies implicating N\textsubscript{2}O. Abbreviations: N\textsubscript{2}O—nitrous oxide; NMDA—N-methyl-D-aspartate; PC-RSC—posterior cingulate-retrosplenial cortex; MS—methionine synthase.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Age</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[30]</td>
<td>Rat</td>
<td>Adult</td>
<td>150% N\textsubscript{2}O</td>
<td>Varied</td>
<td>N\textsubscript{2}O acts similar to NMDA antagonists, suggesting it is also an NMDA antagonist</td>
</tr>
<tr>
<td>[31]</td>
<td>Rat</td>
<td>Adult</td>
<td>150% N\textsubscript{2}O</td>
<td>1–16 h</td>
<td>Vacuoles present in PC-RSC. Maximal at 3 h+ exposure, persistent after 8 h+ exposure</td>
</tr>
<tr>
<td>[32]</td>
<td>Rat</td>
<td>Adult</td>
<td>50% N\textsubscript{2}O</td>
<td>5–80 min</td>
<td>Half-life of hepatic MS inactivation = 5.4 min</td>
</tr>
<tr>
<td>[33]</td>
<td>Human</td>
<td>Adult</td>
<td>70% N\textsubscript{2}O during surgery</td>
<td>30–290 min</td>
<td>Half-life of hepatic MS inactivation = 46 min</td>
</tr>
<tr>
<td>[34]</td>
<td>Human</td>
<td>Adult</td>
<td>Occupational N\textsubscript{2}O exposure</td>
<td>Varied</td>
<td>Increased N\textsubscript{2}O exposure correlates with increased oxidative DNA damage</td>
</tr>
<tr>
<td>[35]</td>
<td>Human</td>
<td>3mo</td>
<td>60% N\textsubscript{2}O during surgery (case study)</td>
<td>45 + 270 min</td>
<td>Severe cerebral atrophy, seizures, and apnoea resulting in death</td>
</tr>
<tr>
<td>[36]</td>
<td>Human</td>
<td>Adult</td>
<td>N\textsubscript{2}O during dental surgery (case study)</td>
<td>Not stated</td>
<td>Progressive numbness and ataxia, treated successfully with vitamin B\textsubscript{12} injections</td>
</tr>
</tbody>
</table>

Fig. 3. Methionine synthase is a ubiquitous cytosolic enzyme that plays a crucial role in the generation of s-adenosylmethionine and in the folate cycle. Nitrous oxide inhibits cobalamin (vitamin B_{12}) from acting as a coenzyme for methionine synthase and thus inhibits the cycle. 5-methyl-THF = 5-methyltetrahydrofolate; 5,10-methylene-THF = 5,10-methylenetetrahydrofolate; THF = tetrahydrofolate. Modified from Weimann\(^9\); with permission from Elsevier.

Methionine Synthase: The Redox Sentinel

Two mechanisms for temporary inactivation of Methionine Synthase:

1. Oxidation of Cobalamin [Cob(I) to Cob(II)]
   - Can occur during each reaction cycle, but usually only 1 out of 100 or less
   - Increased during cellular oxidative stress
   - Increased by environmental toxins and their metabolites
   - Needs either SAM-dependent “repair” or methylB12 replacement
   - Enzyme stays “Off” for a few seconds until cobalamin is repaired
     Allows a few seconds of increased cysteine and GSH synthesis

2. Removal of the SAM-dependent “repair” domain
   - Promoted by sustained oxidative stress
   - Carried out by the ubiquitin/proteasome system
   - Makes enzyme depend upon methylcobalamin and glutathione
   - Enzyme stays “Off” until there is enough glutathione

source: Richard Deth, PhD
Who’s at Risk?

Screening
Exposure to Nitrous Oxide and Neurologic Disease among Dental Professionals

Jay B. Brodsky, MD,* Ellis N. Cohen, MD,† Byron W. Brown, Jr., PhD,‡ Marion L. Wu, MS,§ and Charles E. Whitcher, MD†


Questionnaires, mailed to approximately 30,000 dentists and an equal number of dental assistants requesting information regarding professional exposure to anesthetics and health problems, showed an increased incidence of neurologic complaints in dental professionals who worked with nitrous oxide. The most striking differences were noted in individuals reporting symptoms of numbness, tingling, and/or muscle weakness. For dentists heavily exposed to nitrous oxide, the rate of these complaints was 4-fold greater than for nonanesthetic-exposed dentists. For dental assistants heavily exposed to nitrous oxide, a 3-fold increase in these same complaints was noted. In view of recent evidence that nitrous oxide abuse may lead to polyneuropathy, the results suggest that occupational exposure to nitrous oxide by both dentists and dental assistants may be associated with similar neuropathy.

Key Words: ANESTHETICS, Gases: nitrous oxide; ANESTHESIA: dental; TOXICITY: nitrous oxide.

A NATIONAL Dental Health Survey was recently conducted to determine whether occupational exposure to inhalation anesthetics by dentists and dental chair-side assistants had an effect on health. Detailed description of the general study design and overall results have been presented (1, 2). The present report examines the possibility of specific association between exposure to nitrous oxide (N₂O) and the reported increased incidence of neurologic symptoms and diseases.

these individuals used inhalation anesthetics in their practice. A random sampling of the postcard response was subsequently used to establish two equal size groups representing approximately 15,000 inhalation anesthetic users and 15,000 nonusers.

A 2-page questionnaire that was mailed to each individual asked detailed questions concerning type of inhalation anesthetic agents used, usage by year over a decade (1968–1978), and hours of anesthetic use per week for each year during this period. The
Cobalamins and nitrous oxide: a review

I CHANARIN

From the Department of Haematology, MRC Clinical Research Centre, Harrow, Middlesex, UK

The anaesthetic gas, nitrous oxide (N₂O), once regarded as chemically inert, oxidises some forms of vitamin B₁₂. It does this both when used clinically and in the test tube, and the action is remarkably selective. As far as we know, no other pathway or substance is affected except as a result of damage to vitamin B₁₂. Vitamin B₁₂ that has been oxidised in this way no longer functions as a coenzyme. Thus the effect of N₂O presents the biochemist and haematologist with a remarkable tool with which to explore the mode of action of vitamin B₁₂. It presents the neurologist and neuropathologist with a new probe into the mechanism of vitamin B₁₂ neuropathy, and finally it is a new tool with which to explore the complex field of vitamin B₁₂-folate interrelations.

The purpose of this review is to discuss current work in these fields. No attempt is made to discuss N₂O from the viewpoint of an anaesthetic agent, and the review deals only with the effect on vitamin B₁₂.

Chemistry

*In vitro* a relationship between vitamin B₁₂ and N₂O was demonstrated by Banks et al.¹ and others.² Vitamin B₁₂ is one of a group of transition-metal complexes having a metallic ion linked directly to an organic compound. These are able to activate N₂O, releasing free nitrogen and oxygen. The B₁₂ itself is changed rapidly from the reduced cob(I)alamin or B₁₂₈ form to the oxidised cob(III)alamin or B₁₂₄ form, a change accompanied by rapid conversion of the grey-green colour of cob(I)alamin to a reddish-brown colour due to a mixture of cob(II) and cob(III)alamin. The latter is inactive in such pathways as methionine synthetase, is not more rapid if B₁₂ is supplied, suggesting that new apoenzyme needs to be synthesised.

**Clinical observations**

The first clinical report of toxicity that could be ascribed to N₂O was that of Lassen et al. in 1956,³ who used a 50% N₂O/oxygen mixture as well as other agents to control the spasms in patients with tetanus. Treatment was continued for up to six days. Two of the patients died, and pancytopenias appeared in most of the patients accompanied by megaloblastic haemopoiesis demonstrated by marrow aspiration. The marrow, indeed, was indistinguishable from that in untreated pernicious anaemia. A similar experience was reported in a further case from Australia.⁴ Amess et al.,⁵ in studying the effects of N₂O during and after open heart surgery, found that the marrow was megaloblastic and, by use of the deoxyuridine suppression test, they showed that the pattern of behaviour was similar to that of marrow in untreated pernicious anaemia where there is some return towards normality in the test by the addition of vitamin B₁₂. There was a greater improvement on the addition of folate.

At about the same time reports of a neuropathy in those exposed to excess amounts of N₂O began to appear in the medical literature. By far the largest group were dentists who had developed some addiction to N₂O inhalation, but a dentist and his assistant, who were exposed to N₂O from a leak in defective anaesthetic equipment, were both affected, as was a young lady who obtained her N₂O from capsules designed to produce whipped cream in the home.⁶⁻⁻⁹ The commonest early symptom was numbness and
The decision to use nitrous oxide/oxygen analgesia/anxiolysis must take into consideration alternative behavioral guidance modalities, the patient's dental needs, the effect on the quality of dental care, the patient's emotional development, and the patient's physical considerations. Nitrous oxide generally is acceptable to children and can be titrated easily. Most children are enthusiastic about the administration of nitrous oxide/oxygen; many children report dreaming or being on a "space-ride". For some patients, however, the feeling of "losing control" may be troubling and claustrophobic patients may find the nasal hood confining and unpleasant.

Nitrous oxide has been associated with bioenvironmental concerns because of its contribution to the greenhouse effect. Nitrous oxide is emitted naturally by bacteria in soils and oceans; it is produced by humans through the burning of fossil fuels and forests and the agricultural practices of soil cultivation and nitrogen fertilization. Altogether, nitrous oxide contributes about five percent to the greenhouse effect. Only a small fraction of this five percent (0.35 to two percent), however, is actually the result of combined medical and dental applications of nitrous oxide gas.

The objectives of nitrous oxide/oxygen inhalation include:
- reduce or eliminate anxiety;
- reduce untoward movement and reaction to dental treatment;
- enhance communication and patient cooperation;
- raise the pain reaction threshold;
- increase tolerance for longer appointments;
- aid in treatment of the mentally/physically disabled or medically compromised patient;
- reduce gagging;
- potentiate the effect of sedatives.

Review of the patient's medical history should be performed prior to the decision to use nitrous oxide/oxygen analgesia/anxiolysis. This assessment should include:
1. allergies and previous allergic or adverse drug reactions;
2. current medications including dose, time, route, and site of administration;
3. diseases, disorders, or physical abnormalities and pregnancy status;
4. previous hospitalization to include the date and purpose;
5. recent illnesses (eg, cold or congestion) that may compromise the airway.

Contraindications for use of nitrous oxide/oxygen inhalation may include:
1. some chronic obstructive pulmonary diseases;
2. severe emotional disturbances or drug-related dependencies;
3. first trimester of pregnancy;
4. treatment with bleomycin sulfate;
5. methylenetetrahydrofolate reductase deficiency;
6. cobalamin deficiency.

Whenever possible, appropriate medical specialists should be consulted before administering analgesic/anxiolytic agents to patients with significant underlying medical conditions (eg, severe obstructive pulmonary disease, congestive heart failure, sickle cell disease, acute otitis media, recent tympanic membrane graft, acute severe head injury).

Technique of nitrous oxide/oxygen administration
Nitrous oxide/oxygen must be administered only by appropriately licensed individuals, or under the direct supervision thereof, according to state law. The practitioner responsible for the treatment of the patient and/or the administration of analgesic/anxiolytic agents must be trained in the use of such agents and techniques and appropriate emergency response.
4. Mechanisms of Neurotoxicity

There are various mechanisms which are responsible for its neurotoxic effects, such as NMDA antagonism, enzyme inhibition and alteration of cerebral blood flow. Different brain conditions have different vulnerabilities to each form of toxicity, with neonatal brains more susceptible to NMDA antagonism, vitamin B₁₂ deficient patients more prone to homocysteine mediated problems and the damaged brain often more vulnerable to changes in cerebral blood flow. Because of this, there is a wide range of patients to whom N₂O may have some form of toxicity, with different groups being at greater risks than others. In this way it is extremely important to understand all the needs of a patient before giving nitrous oxide. The danger arises when nitrous oxide is given during dental procedures or as emergency analgesia, e.g., en route to hospital, where underlying problems such as vitamin B₁₂ deficiencies may be undetected. One case study details a patient who presented with weakness in her lower limbs as well as peripheral numbness [36]. MRI scans showed abnormalities on the cervical spinal cord consistent with small lesions. The patient was found to be deficient in vitamin B₁₂ and had been exposed to nitrous oxide for dental surgeries 2–3 months previously. Following 10 months of vitamin B₁₂ injections the symptoms had abated, yet this could have been avoided altogether if nitrous oxide had been avoided for this patient. This highlights the need to fully elucidate nitrous oxide mechanisms of toxicity, so that clinicians can make informed decisions regarding N₂O use. This case is reflected in further case reports involving patients with no prior N₂O abuse experiencing myelopathies following N₂O anaesthesia [48], as well as patients with a history of N₂O abuse [49–52].
polysaccharides, catecholamines and neurotransmitters. Inhibition of methionine synthase will thus result in a reduced concentration of methionine and an elevated concentration of its precursor homocysteine.

Methionine synthase also requires 5-methyltetrahydrofolate (5-methylene-THF) as a cofactor. Tetrahydrofolate (THF) is methylated, via methyl groups donated from the interconversion of serine and glycine, to 5,10-methylene-THF. The enzyme 5,10-methylene-THF reductase (MTHFR) then reduces 5,10-methylene-THF to 5-methylene-THF, which in turn donates a methyl group to cobalamin, forming methylcobalamin and regenerating THF. This process is central to the broader folate cycle which, in turn, is crucial for purine and pyrimidine synthesis. Methylcobalamin is the final methyl donor for methionine synthase.

Folate-cobalamin cycle inactivation has been proposed to be responsible for adverse effects of nitrous oxide as diverse as megaloblastic anaemia, neurotoxicity (including subacute combined degeneration of the spinal cord), immunosuppression, impaired wound healing, and teratogenicity. The elevated homocysteine has been linked to endothelial dysfunction and hypercoagulability and the consequences thereof e.g. perioperative adverse cardiac events and venous thromboembolism.

In addition, hyperhomocysteaemia has been associated with the development of atherosclerosis and its consequences, neurodegenerative diseases/dementia, and potentiation of excitotoxicity.

What is the clinical relevance of these changes though?

There are a number of factors to consider.

Firstly, what level of exposure is required to significantly inhibit the above pathways? Human data suggest that 70% nitrous oxide results in a 50% reduction in methionine synthase activity within 46-90 minutes, with almost no activity being detectable after 200 minutes. Recovery appears to occur within 3-4 days. 

Second, are all patients equally susceptible? It appears not. Most patients have adequate stores of S-adenosylmethionine to see them through the perioperative period. At risk patients include those who are at risk of vitamin B12 or folate deficiency and those with certain genetic profiles.


Thirdly, are any adverse effects time-dependent? The answer is yes in some circumstances; subacute combined degeneration of the cord, for example, is almost exclusively described in long-term nitrous oxide use/abuse. It is not, however, as clear in other situations. Elevated homocysteine levels appear to result in endothelial dysfunction and hypercoagulability in the acute setting. Chronic hyperhomocysteaemia is associated with atherosclerosis and chronic neurological disease e.g. dementia. The exact time scale and range of effects, if any, of elevated

<table>
<thead>
<tr>
<th>Risk factors for B12/Folate deficiency</th>
<th>Nutritional</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption</td>
<td>Vegans</td>
<td>Alcoholics</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>Pernicious anaemia</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Whipple's</td>
<td>Prolonged antacid use</td>
</tr>
<tr>
<td>Ileal resection</td>
<td>Crohn's disease</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Intestinal bacterial overgrowth</td>
<td></td>
</tr>
<tr>
<td>Intestinal parasites</td>
<td>Intestinal parasites</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Risk factors for vitamin B12 or folate deficiency. Modified from Sanders et al.

Certain rare genetic disorders have been associated with adverse outcomes following nitrous oxide anaesthesia, e.g. autosomal recessive MTHFR deficiency! Type III homocysteinuria. These are exceedingly rare, and arguably not really relevant in routine clinical practice. What could be far more relevant, however, are certain fairly recently described, relatively common, single nucleotide polymorphisms (SNP's) of the MTHFR gene. The 677 cytosine-thymidine (677C>T) and 1298 adenine-cytosine (1298A>C) SNP's result in reduced MTHFR activity. Homozygosity for these mutations results in higher baseline plasma homocysteine levels and greater postoperative increases after nitrous oxide exposure compared to both wild-type and heterozygous patients. The clinical correlates of this difference are as yet unknown. These reports are of interest, however, as these mutations are common, with approximately 20% of the Western European population being homozygous for one of the mutations. It must also be pointed out, though, that many non-genetic factors influence homocysteine levels, including drugs (antibiotics, isoniazid, antiepileptics) and medical conditions (hypothyroidism).
Who are at risk for MTHFR mutations?

Prevalence of homozygous TT genotype (two 677C>T alleles) among newborns by area and ethnic background, ICBDMS 2003

Approximately 45% of the population has 1 copy of the MTHFR C677T
### MECHANISMS AND TOXICOLOGY OF NITROUS OXIDE

#### Table 4. Recommended Indications and Contraindications for Nitrous Oxide Use in Anesthetic Practice

<table>
<thead>
<tr>
<th>Indications</th>
<th>Inhalational analgesia/sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute contraindications</strong></td>
<td>Known deficiency of enzyme or substrate in methionine synthase pathway</td>
</tr>
<tr>
<td></td>
<td>Potential toxicity from expansion of gas filled space, e.g., emphysema, pneumothorax, middle ear</td>
</tr>
<tr>
<td></td>
<td>surgery, pneumocephalus, air embolus</td>
</tr>
<tr>
<td><strong>Relative contraindications</strong></td>
<td>Raised intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Prolonged anesthesia (&gt; 6 h)</td>
</tr>
<tr>
<td></td>
<td>First trimester of pregnancy*</td>
</tr>
<tr>
<td></td>
<td>High risk of postoperative nausea and vomiting</td>
</tr>
<tr>
<td><strong>Putative relative contraindications</strong></td>
<td>Risk of myocardial ischemia</td>
</tr>
<tr>
<td>(requiring further investigation)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on the theoretical (but unproven) detrimental effect.

[Link](http://journals.lww.com/anesthesiology/Fulltext/2008/10000/Biologic_Effects_of_Nitrous_Oxide__A__Mechanistic.20.aspx)
At-Risk Populations for Nitrous Oxide

- Oxidative Stress > Glutathione Deficiency and Cell Membrane Damage
- Inflammation > TNFa
- Pathogens > Candida, viral infxns, h pylori . . .
- Heavy Metals
- MTHFR
- MTR
- MTRR
- Low or high homocysteine
- Methionine deficiency
- SAMe deficiency
- B12 deficiency
- MTHF deficiency
- B2 deficiency
- B3 deficiency
- B6 deficiency
- Selenium deficiency
- Cysteine deficiency
- Glycine deficiency
- Glutamate deficiency
“...exposures to chemicals that cause significant depletion of glutathione may ultimately cause a depletion of vitamin B12. In an extreme situation of severely depleted GSH caused by a chemical exposure, typical physiological levels of vitamin B12 may be insufficient to ensure survival of the vitamin...”

$H_2O_2$ inhibits MTR and promotes CBS
Death was from a respiratory arrest on postoperative day 46. Presumably the N₂O induced inhibition of methionine synthetase (see below) in addition to the genetic defect in tetrahydrofolate reductase and led to death secondary to methionine deficiency.

Although as pediatric anesthesiologists one typically thinks of MTHFR and its relationship to homocystinuria, homocystinuria is an uncommon disease, but specific mutations in this gene (single nucleotide polymorphisms, SNPs) are common. One SNP (C>T<sup>677</sup>), for example, is associated with mild homocystinemia, but not deep vein thrombosis. This missense mutation in MTHFR has been associated with preeclampsia.(12) Heterozygosity for this SNP occurs in 12-57% of the population. Lacassie et al. have reported a patient who received N₂O twice within a period of 10 weeks who subsequently developed myelopathy and a macrocytic anemia. Further evaluation showed elevated homocysteine levels, low B<sub>12</sub> levels, and the C>T<sup>677</sup> SNP in MTHFR.(13) Neurologic findings resolved with supplementation with folate and B<sub>12</sub>. Although screening of all patients for elevations in homocysteine plasma levels prior to anesthesia is impractical, with the association of elevated homocysteine levels with coronary disease, more people are having this done. If found, measures of methionine levels might also be considered.(14) If found, fortuitously or otherwise, it must be remembered that close family members may also share this SNP.

When nitrous oxide is no laughing matter: nitrous oxide and pediatric anesthesia
Postoperative dementia: toxicity of nitrous oxide.

Abstract

INTRODUCTION: Post-operative neuropsychiatric manifestations represent a frequent situation and may be due to several aetiologies. The responsibility of vitamin B12 deficiency must be evoked, especially in case of anaesthesia with a currently used substance: nitrous oxide.

CASE REPORT: A 65 year-old man with no medical history, presented problems walking and memory loss 16 days after surgery for femoral prosthesis. Neurological examination revealed paraplegia with syndrome of combined degeneration of the spinal cord. The exploration of cognitive functions showed disorientation in time with memory disorders and disturbance of executive functioning. There was no apraxia, aphasia or agnosia. There were neither psychotic symptoms nor mood changes. MMS was at 18/30. Red blood count revealed an anaemia with macrocytosis (MGV=120 3). Vitamin B12 rate was very low (less than 30 g/l). Folate blood level was normal. Brain MRI showed moderate cerebral atrophy. Other investigations led to the diagnosis of Biermer’s disease (funic atrophy at biopsy with presence in the serum of antibodies to intrinsic factor). The diagnosis of neurological attack related to a vitamin B12 deficiency secondary to Biermer’s disease was established, but the appearance of disorders in the post-operative period suggested the existence of an added factor. The recovery of informations revealed that anaesthesia was maintained by nitrous oxide during two hours and the patient exhibited pre-operative anaemia with macrocytosis. The hypothesis of decompensation of latent vitamin B12 deficiency by nitrous oxide was evoked. Replacement therapy by vitamin B12 induced real improvement of the cognitive impairment. MMS increased to 25/30.

DISCUSSION: Cognitive impairment due to vitamin B12 deficiency is rarely dominated by isolated memory disorders. An authentic dementia is exceptional. Our patient had a dementia diagnosed on the basis of DSM IV criteria including memory disorders, disturbance of executive functioning and significant impairment in social and occupational functioning, associated with a combined degeneration of the spinal cord, common in vitamin B12 deficiency. Furthermore, he had an unknown Biermer’s disease responsible for pre-operative deficiency which was clinically latent (there was only macrocytosis anaemia). The appearance of problems in the post-operative period was due to an acute decompensation of the latent deficiency induced undoubtedly by nitrous oxide used in anaesthesia. According to Christensen, nitrous oxide causes irreversible oxidation of vitamin B12 cobalt’s atom responsible for its inactivation and the appearance of clinical manifestations. Evolution under vitamin B12 replacement therapy depends on the rapidity of its founding. In our case, it led to an improvement, notably in cognitive functions.

CONCLUSION: Through this observation, the authors underline the necessity to search for vitamin B12 deficiency in the case of cognitive features following general anaesthesia.


Tylenol/Acetaminophen

Bad?
Key Points to Take to the Clinic

1. Varying degrees of negative impact
2. Utilize other interventions to reduce anxiety
3. Team care
4. Screen with questionnaire (meds, genes, conditions, age . . .)
5. Inform patients about the risk of nitrous oxide
6. Support methylation prior to giving nitrous oxide – and after.
Thank you

Great ways to stay informed:

- Newsletter Available at www.MTHFR.net
- Facebook: https://www.facebook.com/drbenjaminlynch