# NITROUS OXIDE – DOES IT HAVE A FUTURE?

**Dr Stuart Walker**

Department of Anaesthesia,
Middlemore Hospital, Auckland

## Introduction

In order to have a future it is necessary, but not sufficient, to have had a past and to have a present. Nitrous oxide ($N_2O$) is the only anaesthetic agent which has a past and a present which has spanned the full extent of the age of anaesthesia. Even though the first official demonstration of $N_2O$ was spectacularly unsuccessful, it rapidly established a place in anaesthetic practice which has been unrivalled and unsurpassed to this day. That this has occurred is testament to its efficacy and safety.

The general features of the pharmacology of $N_2O$ including its major adverse effects have been known for a long time, and in spite of these it has continued to be in widespread use since its introduction. Nonetheless in recent years, a number of publications[1,2,3,4] have highlighted the possible deleterious effects of $N_2O$. One of the most influential of these publications (ENIGMA 1) has come from The Australian and New Zealand College of Anaesthetists Clinical Trials Group, and has had a major influence on the use of $N_2O$ in our region. The anticipated publication of ENIGMA 2 will, if positive add fuel to the pyre of $N_2O$, or if negative may allow a reprieve or even perhaps a resurgence.

This presentation will define the past to be from the introduction of $N_2O$ and up to the publication of ENIGMA 1 in 2007. It will consider the present to be from ENIGMA1 to the publication of ENIGMA 2, and define the future as after ENIGMA 2 publication. This presentation will not predict any future past the year 2050. It will concentrate mainly on anaesthetic use, as its' use in obstetric and other forms of analgesia seem relatively secure,[5,6] in spite of the fact that analgesic use is wasteful and polluting.

## The Past

"I am sure the air in heaven must be this wonder-working gas of delight." Robert Southey, Poet (1774 to 1843).

Many of the adverse effects of $N_2O$ are dose related ie the effect is proportional to the degree (concentration and duration) of exposure.

Contrary to widespread belief there is very little evidence that for short, even ambulatory procedures there is any contraindication at all and in fact many under-appreciated advantages.[7] Many of the alternatives, such as increasing concentrations of volatile agent or remifentanil are not without concerns of their own. Ultra-short acting opioids carry the risk of opioid induced hyperalgesia, and chronic post-surgical pain (CPSP), which may actually be ameliorated by $N_2O$.[8,9]

"In the 1990's pain physicians noticed an increasing number of patients being referred to pain clinics because of pain that had started after surgery and which continued for several months or years." (BJA editorial 2013 July). Perhaps the reduction in use of $N_2O$ and the increased observation of CPSP are not coincidental?

The volatile anaesthetics have a greater risk of PONV than $N_2O$ and all options are more expensive than $N_2O$. In a market report of medical gases, "$N_2O$ followed $O_2$ in market share in 2011; however, $N_2O$'s market share is expected to plummet by 2018 due to the availability of anesthetic drugs with high profit margins and the growing use of medical air as an alternative anesthetic gas." See more at Transparency market research.

For longer, inpatient procedures, in sicker patients there is less certainty. In a study of 250 inpatients randomised to 60% $N_2O$ / isoflurane or air / $O_2$ / isoflurane, published in 1990, Eger found no difference in major (eg myocardial infarction, neuronal injury, hypoxaemia, infection, death) or minor (eg nausea, vomiting, headache, earache) untoward outcomes, between the groups, nor a trend to suggest that a larger data cohort would reveal a

significant adverse effect of $N_2O$. The duration of exposure was 1.5-4 hours.[10] Their results support the continued use of $N_2O$.

Others have questioned this position. Badner[4] showed $N_2O$-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischaemia in patients undergoing carotid endarterectomy.

## The Present – ENIGMA 1 (2007)

2,050 inpatients having major non-cardiac procedures were randomised to anaesthesia with or without $N_2O$. Expected exposure to $N_2O$ of 2 hours. The primary outcome (length of hospital stay) was negative. There was increased "severe PONV" in the $N_2O$ group. PONV has been the subject of much anaesthetic research. PONV is easy to study with many possible interventions, and it is clearly of some importance to patients. However it remains a short term problem and not one on which the future of a major plank of anaesthesia should be judged.

A meta-analysis of the effect of omitting $N_2O$ on PONV concludes – "The clinically important risk of major harm (awareness) reduces the usefulness of omitting $N_2O$ to prevent postoperative emesis."[11]

In ENIGMA 1 there were increased risks of "infective" complications (wound infection, pneumonia, pyrexia and atelectasis). There was a trend towards increased cardiac complications, which achieved significance when a subset of patients with cardiac risk factors was identified. This publication was preceded by editorials in the mass media[12,13] and accompanied by an editorial in the same issue of Anesthesiology[14] and almost certainly had profound effects on anaesthetic practice, especially in Australasia.

Subsequent to ENIGMA 1 there have been further publications arising from the original data, and also from other authors which have complicated the picture. In a long term follow up of all ENIGMA patients, Leslie et al[15] found no difference in mortality (19%) or stroke (2.2%) but did show a difference in MI (overall rate 4.5%), the adjusted OR for MI with $N_2O$ was 1.59 (95% CI 1.01-2.51 P0.04).

The publications of Professor Matthew Chan (from the Australian and New Zealand College of Anaesthetists Clinical Trials Group) support the continued use of $N_2O$ because of its effects on chronic post-surgical pain[16] and support the opposite because of its effects on leucocyte DNA and wound infection.[17] Post-hoc analyses of large trials of anaesthesia such as POISE and GALA in patients with, or at risk of vascular disease, have both failed to show any cardiac risk attributable to $N_2O$.[18,19] The VINO trial similarly has not shown any increased cardiac risk with $N_2O$.[20]

Finally, $N_2O$ is both a greenhouse gas and causes ozone depletion.

$N_2O$ from medical use is less than 1% of anthropogenic $N_2O$ which is in turn less than 5% of the anthropogenic climate change effect. Sadly, abolition of medical $N_2O$ would have no effect on climate change.

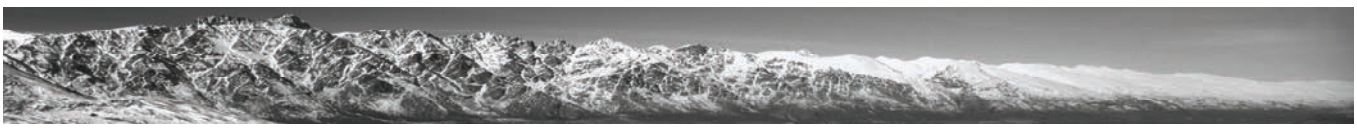
## The Future

An informal survey of 100 consecutive inhalational anaesthetics from our department in 2012 showed only 9 patients received $N_2O$.

We need to recognise that we are a tiny minority of the collective opinion of the global anaesthetic community. A recent analysis of the Cleveland clinic database showed that $N_2O$ was used in 16,961 patients out of 49,016 between 2005 and 2009, with no deleterious effect. In spite of their conclusion that the results of this study do not support eliminating $N_2O$ from anaesthetic practice there was a definite trend towards reduced use of $N_2O$ over the 5 year period[21] (see Healthcare research analytics).

Healthcare Research and Analytics Operating Room Audit (accessed August 13, 2012), also shows $N_2O$ use has declined in the United States, utilised in 33% of all general anaesthetics given in 2009 but only 21% of those in 2011.

Data from the POISE re-analysis shows that the use of $N_2O$ in patients at risk of cardiac complications varies from 5% of general anaesthetics given in Central and South America, up to 80% in India. Given the problems of providing affordable health care to a global population today of over 7 billion citizens, and even more importantly



projected to reach 9 billion by 2050, it would seem $N_2O$ may well have a future even in patients at risk of cardiac events, regardless of the opinions of any of us.

If ENIGMA 2 confirms all the findings of ENIGMA 1, then the dilemma that positive effects from $N_2O$ on CPSP must be balanced against the risks of increased cardiac and infective complications remains. Anaesthetists will be left to consider the relative risks and benefits according to the patient's risk profile and the duration of exposure. It may be that $N_2O$ may need to be given only for the first hour or two of anaesthesia in order to prevent central spinal cord sensitisation and limit the risk of infective complications and vascular risks of hyperhomocystinaemia.

With more information it may be we can use $N_2O$ in a more knowledgeable way to gain the benefits and limit harms and retain $N_2O$ as the anaesthetic "stock in the stew" in the foreseeable future. In patients at low risk of vascular events having moderate or short duration procedures, which still make up the vast majority of routine surgery, there should be no reason not to take advantage of the economic and clinical benefits of $N_2O$.

For those at high risk of PONV (Apfel score 4) it may be wise to avoid inhalational anaesthesia. For those at moderate risk of PONV, the decision to use $N_2O$ would be more complex. For example, the risk of PONV with 2 prophylactic anti-emetics would need to be balanced against the risk of CPSP and perhaps the patient should be informed of the relative risks and benefits for full informed consent.

## References


1. Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery Myles et al. Anesthesiology 2007; 107:221–34
2. Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. Nagele P et al. ANESTHESIOLOGY. 2008; 109:36–43.
3. Adverse effect of nitrous oxide in a child with methylenetetrahydrofolate reductase deficiency. Selzer et al *N Engl J Med* 2003; 349: 45−50
4. $N_2O$-Induced Increased Homocysteine Concentrations Are Associated with Increased Postoperative Myocardial Ischemia in Patients Undergoing Carotid Endarterectomy. Neal H. Badner, et al Anesthesia & Analgesia Nov 2000.
5. Inhaled intrapartum analgesia using 50%$N_2O$ in a low income hospital setting. Pita et al Arch Gynecol Obstet 2012 286, 627-31.
6. Nitrous oxide in emergency medicine. O' Sullivan, J Benger Emerg Med J 2003;20:214–217.
7. $N_2O$ in ambulatory anaesthesia. Smith I Curr Opin Anesthesiology 2006 19. 592-6.
8. $N_20$ reduces OIH after remifentanil-propofol anaesthesia in humans BJA Sept 2011.
9. Increase in chronic pain in post thoracotomy patients given remifentanil BJA Oct 2012.
10. Clinical pharmacology of N2O: an argument for its continued use EI Eger 2d, et al Anesthesia & Analgesia 1990, 71 591.
11. Omitting $N_2O$ in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Tramèr M, Moore A, McQuay H. Br J Anaesth 1996; 76:186–193.
12. Nitrous oxide anaesthetic unsafe, say researchers New Zealand Herald. May 5 2005.
13. Safety of laughing gas no joke. Sydney Morning Herald. Aug 9 2007.
14. Is It Time to Retire High-concentration Nitrous Oxide? Anesthesiology 107(2), August 2007, pp 200-201.
15. $N_2O$ and Long-Term Morbidity and Mortality in the ENIGMA Trial. Leslie, Kate et al Anesthesia & Analgesia 112(2), February 2011, p 387–393.
16. Chronic postsurgical pain after nitrous oxide anesthesia Matthew T.V. Chana, et al. Pain 2011 152 2514-20.
17. 17. Leukocyte DNA Damage and Wound Infection after N2O Administration Chen et al. Anesthesiology 2013;118:
18. $N_2O$ and Serious Morbidity and Mortality in the POISE Trial. Leslie, Kate et al Anesthesia & Analgesia 116(5), May 2013, p 1034–1040.
19. $N_2O$ exposure does not seem to be associated with increased mortality, stroke, and myocardial infarction: A non-randomized subgroup analysis of the General Anaesthesia compared with Local Anaesthesia for carotid surgery (GALA) trial. Sanders RD et al. Br J Anaesth. 2012;109:361–7.
20. Vitamins in $N_2O$ (VINO) randomized trial. Nagele P et al. Anesthesiology 2013;119:19–28.
21. The Association Between $N_2O$ and Postoperative Mortality and Morbidity After Noncardiac Surgery. Turan, et al Anesth Analg 2013;116:1026–33