

Nitrous Oxide Self-Administered from a Demand Valve for 4-Minute Period: Dose-Effect on Attention, Mode and Wakefulness

Per Blom, Michael H. Silverman, Roy S. Fishman and Jan G. Jakobsson*

Karolinska Institute, Institution for Physiology & Pharmacology, Department of Anaesthesia, Danderyds University Hospital, Stockholm, Sweden

Abstract

Nitrous oxide is unique in that it is none-invasive and has a rapid onset of action, making it a valuable option in a variety of emergent situation and in painful paediatric procedures. The present randomised controlled study was set up in order to explore the effects of 3 different concentrations of nitrous oxide, 40, 55 and 70 vol. % as compared to placebo, provided by self administered from a demand valve by healthy volunteers for a short 4-minute period evaluating effect on attention, mode and wakefulness.

Onset time and peak reduction in attention, change in saccadic eye movements, showed a dose dependent pattern. After brief use, saccadic eye movements returned to baseline within minutes after cessation of administration. Loss of consciousness was observed only during administration of the 70 vol. %, minor side effects such as dizziness and nausea was observed during inhalation of all three active treatments.

The risks for over sedation/unconsciousness has to be weighed against the clinical benefit of faster and more pronounced effects if a 70 % fixed nitrous oxide concentration is to be used by self administration from a demand valve.

Keywords: Nitrous oxide; Attention; Sedation; Saccadic eye movements

Introduction

Nitrous oxide has been used for pain relief and sedation for decades. It is unique in that it is none-invasive and has a rapid onset as well as offset of action. Considerable clinical experience with nitrous oxide analgesia has been gained with the use of premixed nitrous oxide and oxygen 50 vol. % concentrations each since being introduced in the early 1960-ties [1]. The 50:50 pre-mix has gained increased clinical use for sedation and relaxation for decades [2-4]. During the last few years nitrous oxide and oxygen mixture has also gained a "renewed" interest especially as a safe and effective alternative for procedural management in children [5-7]. For short procedures with need for a peak-effect such as intravenous cannulation, injections, biopsies, fracture reposition, urinary catheterisation, removal of foreign bodies, both time to onset of action and offset of drug effects are of importance.

The aim of the present study was evaluating the effects of 3 different concentrations of nitrous oxide mixed with oxygen, as compared to placebo, when administered for a maximum of 4 minutes on attention, mode, and wakefulness.

Methods

We studied 16 healthy volunteers after ethical committee and local review boards approval of the study protocol. Eight male and 8 female subjects took part in the study. The subjects had a mean (SD) age of 40.6±5.70 years (range 36 to 57 years), a mean (SD) height of 1.728±0.0910 m, a mean (SD) weight of 74.2±10.77 kg and a mean (SD) BMI of 24.75±2.225 kg/m².

All study subjects were instructed to refrain from taking any drugs or alcohol for 24 hours prior to study.

A randomized, placebo controlled design was used in which subjects were exposed to 40% N₂O mixture, 55% N₂O mixture, 70% N₂O mixture or placebo (oxygen in air) during each of the 4 study sessions. A crossover design was used so that each subject had received all treatments by the end of the study. All treatments active as well

as "placebo" oxygen in air were inhaled for a maximum of 4 minutes each. Sessions were separated by at least 4 days for proper wash-out. Randomisation was done by sealed envelopes. Following appropriate familiarisation and training, all treatments were self-administered by subjects, under medical supervision, using a facemask and demand-valve apparatus. All subject kept the mask them self, one of the unique safety aspects of the fixed mixture administered by a "demand valve" is that "if over-sedated" the subject will automatically lose control and subsequently not be able to keep the mask tight enough to open the demand valve, thus no further gas will be administered. Gas composition was blinded to study subject as well as personnel involved in supervision and testing.

Evaluation of effects

All study subjects and personnel involved in testing were blinded to study gas.

Evaluation of gas equilibration was done by conventional end tidal nitrous oxide concentration measures with an OscarOxy (Datex Ohmeda, Helsinki, Finland). End tidal nitrous oxide concentration was recorded electronically every 30 seconds during each period of dosing. The end-tidal gas concentrations were measured and recorded by a dedicated technician otherwise not involved in the study. The anaesthetic gas monitor display was placed outside of the study room.

*Corresponding author: Jan Jakobsson, Associate Professor, Department of Anaesthesia, Karolinska Institute, Danderyds University Hospital, Stockholm, Sweden, E-mail: jan.jakobsson@ki.se

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Saccadic Eye Movements was used as an objective surrogate test for evaluation of attention [8]. Eye movements were measured using specially designed electrodes positioned between the upper and lower canthus of each eye and linked to a centrally positioned reference on the forehead. Subjects were required to move their eyes to look at lights, which were presented at intervals on a light bar in front of them. Tests were conducted in the sitting position in a reclining chair. Eye movements were measured within 30 minutes prior to dosing of each study gas mixture, every minute during the inhalation period, immediately following the end of the inhalation period and at 1, 2, 4, 6, 8 and 10 minutes from the end of the inhalation period.

The Bond and Lader Questionnaire, was used for evaluating subjective experience during inhalation, assessing sedation, anxiolysis and relaxation [9]. This was performed using PenScreen hand-held computers and comprised a series of bipolar, visual analogue mood scales (VAMS) consisting of 100 mm lines by which the subject's feelings at any given time can be self-rated. The scales appeared on the screen one at a time and subjects rated their feelings by putting a perpendicular mark across each of the lines, before tapping "ok" to move onto the next scale. Scores are automatically measured in millimetres from the left-hand end of each line to the mark and from this 3 sub-scores for anxiety, dysphoria and sedation can be calculated. Mode evaluations were performed within the 30-minute period prior to dosing, immediately following the end of the inhalation period and 15 and 30 minutes after the end of the inhalation period. A blinded observer also noted degree of sedation during administration during administration. Evaluation of subjective effects were performed at 4 minutes in all subjects regardless of whether they had been inhaling the test gas for the entire 4 minute session.

All side effects experienced during and after inhalations were asked for and recorded by a devoted research nurse.

Statistics

This is an explorative study and no formal power analysis has been conducted. All data is given as mean and standard deviation unless otherwise stated. No testing between groups was performed because of the explorative nature of the study.

Results

The end-tidal nitrous oxide concentrations showed a dose related pattern with regard both to peak value and the time to reach the peak see (Table 1). The mean end-tidal nitrous oxide concentration for

	Mean C _{max} (%)	tmax (secs)
40 % Nitrous Oxide	31	190
55 % Nitrous Oxide	38	140
70 % Nitrous Oxide	49	90

Table 1: Mean Time to peak and Peak end tidal nitrous oxide concentrations for the 3 gas mixtures studied.

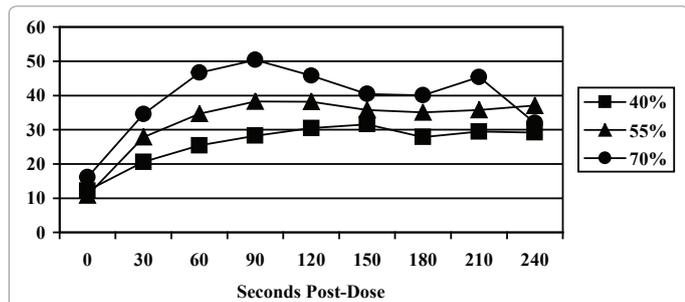


Figure 1: End-tidal nitrous oxide concentrations for the 3 active gas mixtures studied (vol.%)

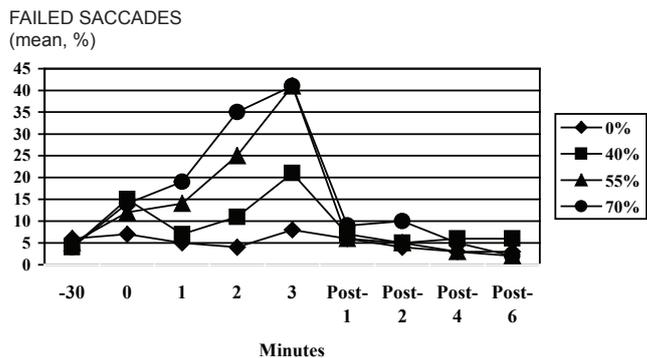
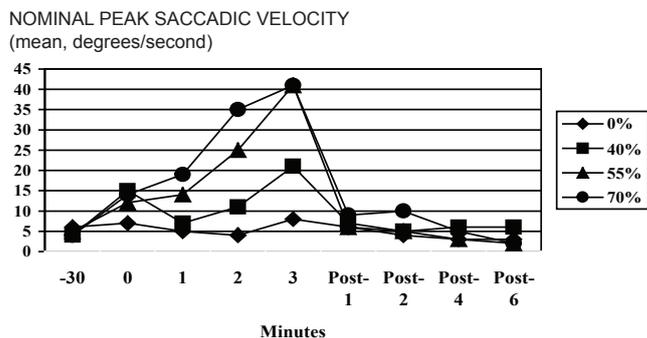


Figure 2: Saccadic eye movements studied during a 240 seconds self-administration

	Mild	Moderate	Severe	Unconscious
70 vol. %	2	20	3	6
55 vol. %	7	16	1	0
40 vol. %	18	2	0	0

Table 2: Observers assessment of Sedation in relation to nitrous oxide concentration

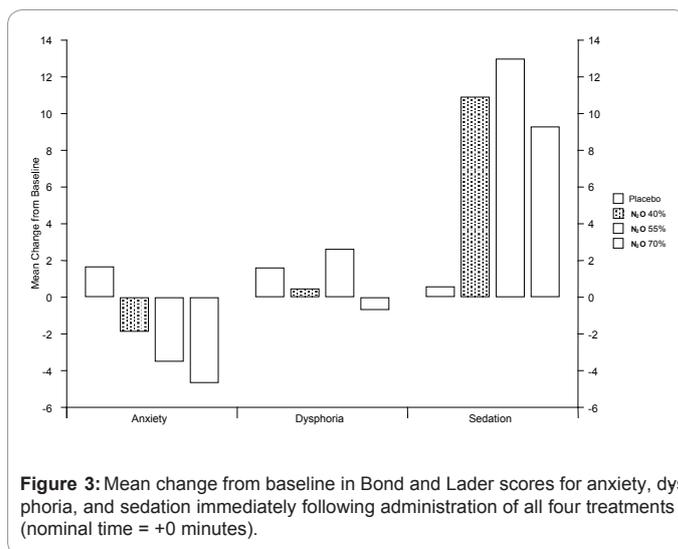


Figure 3: Mean change from baseline in Bond and Lader scores for anxiety, dysphoria, and sedation immediately following administration of all four treatments (nominal time = +0 minutes).

the 55% and 70% N₂O treatments decreased after about 90 seconds, particularly for the 70% treatment (Figure 1). This was due to that some subject becoming drowsy and unable to hold the mask tight enough to have a gas flow delivered from the demand valve before the end of the 4-minute dosing period.

Following an initial small increase in peak saccadic velocity (PSV) at the start of dosing, probably due to an increase in attention, a clear dose-dependent decrease in PSV and increase in number of failed saccades was observed (Figure 2). The 55 and 70 % nitrous oxide concentrations caused more or less the same effects while the 40 % did not reach the same magnitude of reduction of attention. In most subjects both PSV and number of failed saccades returned to pre-dose levels within minutes post-inhalation. PSV values remained consistent on placebo treatment during all phases of the experiment.

All doses studied produced an increase in sedation both assessed by the observer and the study subjects at the end of the inhalation period (Table 2 and Figure 3). The subjective rating of sedation was seemingly similar for all active treatments; all active treatments displayed a small decrease in anxiety level following drug administration Figure 3.

All drug effects diminished rapidly after end of administration, saccadic eye movements were back on base-line values within minutes (Figure 2).

No serious adverse events were noticed during or following administration. Dizziness and somnolence were the most commonly reported adverse events. Following administration of the 70% four of the 16 subjects lost consciousness, in 2 on two occasions. Consciousness was rapidly regained following the stop of self-administration without any further interventions.

Discussion

The primary objective of this pilot study was to investigate the effects of 3 different concentrations of N₂O mixed with oxygen, when administration for a short, maximum 4-minutes, period. This short dosing period was chosen for assessment both in order to mimic an emergent situation where fast and intense effects are sought but also as a reduced dose would benefit occupational exposure and environmental related N₂O burdens. No statistical analysis was conducted due to the limited number of subjects studied and lack of background data. Our results may still be considered expected: we found that increasing the nitrous oxide concentration affected both peak end-tidal concentrations, time when this was reached and the magnitude of psychometric effects. The raise in end tidal concentration was almost twice as high in the 70 % group compared to the 40 % concentration. The high, 70 vol. %-mixture, was also associated to more sedation causing self-regulated cessation of administration due to the self-administrative mode of delivery on several occasions. Also the objective measure of attention, saccadic eye movements, showed dose dependent changes. The subjective ratings of effects did however not show any obvious clinical difference between the three doses tested. It is however of importance to recall that this study was performed in healthy volunteers in a laboratory setting without any noxious or distressing stimuli. The mode and attention effects from nitrous oxide have been previously studied. Zancy et al. [10] looked at the subjective effects from nitrous oxide in concentrations ranging from 40 – 80 vol.% after only four breaths and found clear dose dependent effect on mode and psychomotor performance with a similar fast return to base-line following cessation of administration [10]. One may argue that the tests chosen although used in other studies of medication effects are not optimal to separate clinically meaningful subjective effects from nitrous oxide [11].

Saccadic Eye Movement (SEM) assessment has been suggested as a robust measure for assessing the time course of effects on attention and indirect on sedation in relation to dose [8,12]. We found clear dose-dependent decrease in peak saccadic velocity and increase in number of failed saccades. For the high 70 % the effects were both more rapid and profound than for the lower concentrations. The rapid return to baseline already within minutes after cessation of nitrous oxide administration seen can be taken much in line with the current drug company recommendation to allow some 30 minutes to elapse before

allowing patients to drive and or to do other complex and potential hazardous tasks. Our results are in line with Magnusson et al they also found dose dependent reduction in peak velocity of voluntary saccades [13]. They saw however a somewhat slower recovery. By 10 min after exposure to nitrous oxide, the peak velocity of voluntary saccades had recovered but had not reached pre-test values. We measured peak saccadic velocity, there have been arguments that the velocity changes are less sensitive compared to the saccadic eye movement latency [14].

It is of course a major limitation that the analgesic components were not investigated and one has to have in mind that we studied volunteers, without anxiety, pain or other distressing factors. The analgesic effect of nitrous oxide has, however been studied in several studies showing significant effect already at 0.2 of minimal alveolar concentration (MAC) equivalents (20 vol.%) nitrous oxide [15-18].

Nitrous oxide used in fixed combination with oxygen self-administered from a demand valve seems reassuringly safe, the 70 % concentration was however associated with extensive sedation and even loss of consciousness in a number of subjects. This is a finding in line with earlier reports, showing MAC-awake of about 60 vol. % [15,19]. Even if the impaired consciousness was rapidly reversed as a result of the incapacity to hold the mask tight and thus open the demand valve. The risk associated with loss of consciousness and potentially reduction in protecting reflexes calls for a certain degree of caution. Loss of consciousness increase the risk for more fearful events if occurring under less controlled circumstances.

The findings of this explorative study, within the limitations described above, suggest that an increase in concentration administered for a short duration of 4-minutes only may provide benefits to the patient. Further studies are needed in order to define whether there are any clear clinical benefits in increasing the fixed nitrous oxide concentration for short duration administration compared to the well-established 50:50 mixture.

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