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NITROUS OXIDE. SHOULD IT STILL BE USED IN PEDIATRIC MEDICINE? (PART 1)

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ЗАКИСЬ АЗОТА. НУЖНА ЛИ ОНА НАМ ПРИ ПРОВЕДЕНИИ АНЕСТЕЗИИ У ДЕТЕЙ? (ЧАСТЬ I)

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Nitrous oxide (N₂O) has been used in medicine for more than 165 years. By incidence was the analgesic effect recognized by Howard Wells. Originally was it thought to be a clean and anesthetic not causing a single adverse effect, and therefore was it considered the safest anesthetic. However, around 1956 was it recognized that some patients, after prolonged exposure developed, mostly transient, megaloblastic anemia and neurological disorders. Gradually became adverse effects more known. This resulted in discussions in the literature on the safety of N₂O. Since the 1990’s are there indications that N₂O administration in children during the period of brain development and in elderly persons has neurotoxic effects. This lead to the conclusion of many that N₂O should no longer be used in medicine. However, other physicians have the opinion that there is no reason to stop the use of N₂O.

*Keywords: pediatric anesthesia, children surgery, anesthesia associated complications in children, drugs adverse reactions*

Закись азота (N₂O) применяется в медицинских целях более 165 лет. Ее аналгетический эффект был случайно обнаружен Говардом Веллсом. Изначально считалось, что это достаточно безопасный анестетик, не вызывающий побочных реакций. Однако начиная с середины 1950-х годов было замечено, что у ряда пациентов, получавших этот анестетик, развивались преходящие неврологические расстройства и гемолитическая анемия. Постепенно все больше количество побочных эффектов данного препарата было замечено при его практическом применении. В 1990-х годах было показано, что его использование у детей в период развития головного мозга, а также у пожилых пациентов приводит к развитию нейротоксических эффектов. Это привело к широкой дискуссии относительно использования закиси азота ввиду его небезопасности для пациентов и персонала, а также к заключению о нецелесообразности использования закиси азота. Однако не менее обширная когорта медицинских профессионалов не видит оснований для прекращения применения закиси азота в своей практике.

*Ключевые слова: педиатрическая анестезия, детская хирургия, осложнения анестезии у детей, побочные эффекты лекарственных средств*
1. Introduction
For more than 170 years has nitrous oxide (N₂O) been used in medicine, after in 1772 the British chemist Joseph Priestley (1733–1804) had discovered the gas [1]. There are, however, some indications that Joseph Black (1728–1799), Scottish physician, was first to prepare N₂O. This translates in the chemical reaction:
\[ \text{NH}_4\text{NO}_3 \rightarrow \text{N}_2\text{O} + 2\text{H}_2\text{O}. \]
In 1799, Scottish physician, was first to prepare N₂O. This was the Medical Pneumatic Institution of the British physician Thomas Beddoes (1760–1808) in Hotwells near Bristol, England. This institute was a medical research facility whose aim it was to investigate the possible therapeutic uses of newly-discovered gases and chemicals to treat diseases of the lung. Many people came to the Medical Pneumatic Institution to enjoy the effect of N₂O under the restriction that they had to write down the experienced effect of N₂O. Because of this and other experiences indicated Davy already the possible use in anesthesia.

In 1823 was N₂O-gash liquefied by the British physicist-chemist Michael Faraday (1791–1867). He had in 1818 already demonstrated that inhalation of ether produced anesthetic effects similar to those of nitrous oxide. After successful trials in Hartford, in Boston it’s public demonstration was considered by most observers to be a failure, because the volunteer cried during tooth extraction. Because of this, and the disappointing effect of N₂O and ether, the Indian Institute of the British physician Thomas Beddoes (1760–1808) was considered by most observers to be a failure, because the volunteer cried during tooth extraction. Because of this, and the disappointing effect of N₂O and ether remained N₂O widely used. The use of N₂O for tooth extraction became so popular that dentists advertised with it in the newspapers and on billboards. In 1864 starvation in England, the British physician-anesthetist his lecture ‘On the physiological action of nitrous oxide’ for the Odontological Society of Great Britain [5]. He found that N₂O was neither a true analgesic nor a true analgesic, and that the effect is on the state of anesthesia, was it recognized that N₂O possibly acts on a variety of such receptors. Currently is it indeed known that there are various mechanisms involved in the effect of N₂O. A direct modulation of a broad range of ligand-gated ion channels of N₂O has been demonstrated. N₂O showed to have an inhibitory action at N-methyl-D-aspartate (NMDA) glutamate receptors, while it has a stimulatory activity at dopaminergic, a1 and a2 adrenergic and opioid receptors. It further moderately blocks β2-subunit-containing nicotinic acetylcholine channels, it almost insignificantly inhibits AMPA, kainate, GABAA, and 5-HT3 receptors, and slightly potentiates GABAα and glycine receptors [6]. It has also been shown to activate transiently-activated channels, such as BK, T-type calcium channels, N₂O may act to imitate nitric oxide (NO) in the central nervous system, and this may be related to its analgetic and anxiolytic properties. However, still is there much unknown on the real mechanism of action of N₂O.

The analgesic effect of N₂O is much stronger then its anesthetic effect. Nitrous oxide activates supraspinal opioid receptors. It was Raymond Quinney and his colleagues whom, at the Children’s Hospital of Wisconsin, have demonstrated that it acts on the complex of opioid receptors in the brain and spinal column, and that this action produces analgesic and euphoric effects [7, 8]. The analgesic effect is inhibited by Naloxone and similar compounds [10, 11]. The μ- and κ-opioid receptor are likely the places where N₂O acts [12]. In a study were μ-receptors competitively inhibited by N₂O while μ-receptors were non-competitively bound [13]. A study where it was used as analgesic for insertion of intraurethral devices in nulliparous women proved its insufficiency as analgesic [14]. Nitrous oxide stimulates release of enkephalins, which bind to opioid receptors that trigger descending noradrenergic pathways [15]. Its anesthetic, hallucinogenic, and euphoric effects allow for lower N₂O concentrations to be used. Since then was N₂O part of the armamentarium of the anesthetists, mainly as a carrier gas for other volatile anesthetics. It also got a place in obstetrics where an equal mixture of N₂O and oxygen became used under the name Entonox. Since then millions of people have received N₂O as a so-called harmless anesthetic, without awareness of its adverse effects. Until 1956 has N₂O thus been regarded as a totally safe drug, but then some reports on adverse hematologic and neurologic effects were published. First with repeated recreational exposure, and thereafter with even limited clinical re-exposure as a sedative in the treatment of tetanus. Although originally suspected to apply to only a small number of children with specific types of metabolic inborn errors, it has become apparent that these metabolic abnormalities can be present in a far larger number of individuals. Then started the discussion whether we should still use N₂O in medicine, because other techniques and better and shorter acting other drugs became available.

N₂O nowadays is not only used in medicine, but also in other areas. In industry, N₂O is used as an oxidizer in atomic absorption spectrometry and in the manufacture of semiconductors. In the dairy industry, N₂O is used as a bacteriostatic, tasteless, odorless food processing propellant. N₂O is also injected into the air intake of car engines by racing enthusiasts to boost horsepower. N₂O is also used to pre-condition engines for deep water testing, because it mimics the disorientation and behavioral changes of decompression illness (the ‘bends’) when a diver surfaces from the depths too rapidly.

2. Mechanism of action of nitrous oxide
The mechanism of action of N₂O despite its long time use in medicine is still not completely understood. Only after the discovery that a number of receptors and transmitters are involved in consciousness and in reaching the state of anesthesia, was it recognized that N₂O possibly acts on a variety of such receptors. Currently is it indeed known that there are various mechanisms involved in the effect of N₂O. A direct modulation of a broad range of ligand-gated ion channels of N₂O has been demonstrated. N₂O showed to have an inhibitory action at N-methyl-D-aspartate (NMDA) glutamate receptors, while it has a stimulatory activity at dopaminergic, a1 and a2 adrenergic and opioid receptors. It further moderately blocks β2-subunit-containing nicotinic acetylcholine channels, it almost insignificantly inhibits AMPA, kainate, GABAA, and 5-HT3 receptors, and slightly potentiates GABAα, and glycine receptors [6]. It has also been shown to activate transiently-activated channels, such as BK, T-type calcium channels, N₂O may act to imitate nitric oxide (NO) in the central nervous system, and this may be related to its analgetic and anxiolytic properties. However, still is there much unknown on the real mechanism of action of N₂O.

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disembodied state where even fundamental qualities such as time and space drift loose from their moorings.

Current research thus indicates that the analgesic effect of N2O appears is initiated by stimulated neuronal release of endogenous opioid peptides, with subsequent activation of opioid receptors and descending GABAergic pathways that modulate nociceptive processing at the spinal level [17]. The anxiolytic effect of N2O involves activation of the GABA<sub>A</sub> receptor through the benzodiazepine binding site, although whether N2O acts directly or indirectly upon the latter targets remains uncertain. The anxiolytic pathway that is stimulated includes a segment that involves a sequence of 3 key effects: i.e. inhibition of NMDA glutamate receptors and removing its excitatory influence in the nervous system.

3. The adverse effects of nitrous oxide

Beginning in 1956, several reports appeared implicating that nitrous oxide is involved in the development of methemoglobinemia or neurologic findings similar to those of megaloblastic anemia and B12 deficiency [18, 19, 20, 21, 22]. It occurred after relatively long administrati-

4. Inactivation of vitamin B12

N2O has been also implicated in the adverse effects on health seen in those individuals who are chronically exposed to trace amounts of the drug [23, 24]. Especially in area’s where ventilation of the room is less adequate as in operating theaters or where scavenging of exhaled gases is not used (recovery rooms, obstetric rooms, dental practices, patient wards, etc.). Adverse effects were especially described in dentistry [25]. These adversities include infertility, spontaneous abortion, testicular changes, decreased sperm count, blood dyscrasias, and hematologic and neurologic deficits. In 1986 it was concluded that N2O can lead to many adverse effects i.e. hypoxia, inactivation of vitamin B12, hemato-

5. Inactivation of vitamin B12

With 33 % oxygen was far more pleasant then 100 % N2O. Also Edmund Andrews (1822–1904), American surgeon whom was taught the technique by Rogers, suggested in 1868 to add 20 % oxygen to the inhalation of N2O to avoid hypoxia and make anesthesia safer [38]. In anesthesia is 70 % N2O and 30 % oxygen the usual concentration admi-

6. Diffusion hypoxia and filling of gas containing compartments

When a patient’s inspired gas mixture is switched from air containing approximately 78 % nitrogen to an anesthetic mixture containing 70 % nitrous oxide, will the nitrous oxide enter gas-filled spaces more than 30 times faster than nitrogen can exit the space. As a result, the volume or pressure within such a space will increase. Thus blood passing a nitrogen-filled gas space within the body can deliver a greater volume of nitrous oxide to the space than the volume of nitrogen it removes from the space. But also does it result in increase of either the volume of, or the pressure within gas filled body spaces [39, 40]. A doubling or tripling of volume of gas-filled spaces can occur. Cuff pressures of endotracheal tubes and laryngeal masks air-

7. Diffusion hypoxia and filling of gas containing compartments

The rapid exit of N2O from the alveoli causes remaining alveolar gases to be concentrated, thus accelerating the uptake of volatile agents into the blood and speeding the onset of anesthesia (second gas effect) [59, 60]. At the end of anesthesia, the more rapid elimination of nitrous oxide decreases the partial pressure of oxygen in the lungs, an effect known as diffusion hypoxia. For this reason, it is conventional practice to provide the patient with 100 % oxygen during the first few minutes following discontinuation of nitrous oxide. Hypoxemia is significant for only a matter of minutes and has disappeared completely only when high concentrations (70 %) have been de-

8. Inactivation of vitamin B12

In 1967–1968 was it found by biochemists that N2O inactivates cobalamin (vitamin B12) by oxidation [51, 62]. This result was not appreciated in the medical community where it was only recognized in 1978 [63]. In 1982 it was demonstrated in patients’ liver biopsies after exposure to 50–70 % N2O for 1.25–2.75 hours, that there was a decrease in methionine synthase [64]. Cobalamin is a co-enzyme of methionine synthase, which is essential for the production of methionine and the
production of methyl groups. Methionine is an important amino acid that serves as a methyl donor via its activat-
formed S-adenosyl-methionine in hundreds of bio-
logic reactions, in the production of DNA, RNA, myelin and catecholamines amongst others. The end product of
methionine demethylation is homocysteine, whose remethylation is catalyzed by the vitamin B12-dependent enzyme
methionine synthase. Hyper-homocysteinemia, cumulation of folic acid and a shortage of methionine are the
result of methionine synthase inhibition [65]. Homocysteine has been shown to act as an agonist on the glu-
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contradictory, the elderly, and the malnourished [70]. The duration of administration and concentration of N2O are important factors in the inactivation of vitamin B12 [71]. The authors found that in rats 50 % N2O exposure decreased methi-
one synthase activity within 30 min, and the activity was virtually undetectable after 6 h. Since N2O readily passes the placenta is also the fetus affected. In 1985 was it for the first time demonstrated that an adverse influence of N2O on vitamin B12 metabolism and DNA synthesis exists also in humans [72]. Exposing rats to N2O for 2 hours revealed in a 50 % reduction of methionine synthetase. Mice, pigs, and rats exposed to N2O have delayed recovery of enzyme activity for periods of four days or more [73, 74, 75, 76]. De novo synthesis of the enzyme is required to restore activity and takes several days [77]. Deficiency of vitamin B12 typically results in degeneration of poste-
rior and lateral columns of the spinal cord, because it is essential in the production and maintenance of myelene. Clinical symptoms include sensory neuropathy, myelo-
pathy, and encephalopathy; they can occur within days or weeks after exposure to N2O anesthesia in people with subclinical vitamin B12 deficiency. In humans, the mean half-time for hepatic methionine synthase inactivation by 1 atmosphere N2O is approximately 1 hour (or 0.5 atmo-
ospheres for 2 hours), with less than 20 % residual activi-

ty after 2 atmosphere-hours of exposure [78]. However, others found 50 % reduction after exposure for 40 minutes to 50 % N2O [79]. This last time span is well within the duration of most medical procedures. The authors found complete inactivation 200 minutes after the start of admin-
istration. A second exposure during this interval may be especially harmful because it prolongs the period of dimin-
ished methionine synthase activity. Repeated use of N2O depresses stores of vitamin B12 even in healthy people. Health care workers are frequently exposed to N2O and may develop all adverse effects of it [80, 81]. Also non-health care workers exposed to N2O can experience adverse effects [82]. Preoperative treatment with folic acid prevented the development of methionine synthase deficiency in them [83].

3.4. Cognitive and behavioral disturbances
It was demonstrated in rats that decrease in cortical me-
thionine synthase concentration due to N2O causes lasting impairment of memory [84]. Others demonstrated that exposure to N2O may result in short-term behavioral effects and may decrease mental performance, audiovisual ability and manual dexterity. It also can cause mood changes, psychosis, auditory and visual hallucinations, and violent behavior [85, 86, 87, 88, 89, 90]. Presentation as a con-
version disorder with myeloneuropathy was published [91]. N2O in sub anesthetic concentrations produces some subjective effects that are characteristic of psychedelic drugs, i.e., changes in body awareness and image, alterations of time perception, and experiences of a dreamy, detached reverie state [92]. Also diminished cognitive
motor proficiency results from inhalation at sub-anesthetic concentrations [93]. In a study in volunteers it was found that the subjects became more confused, sedated, ‘‘high’’, dysphoric, and stimulated during inhalation of 40 % nitrous oxide than with the inhalation of 20 %; fatigue, depression and anxiety increased as soon as inhalation of 40 % nitrous oxide had ceased [94].

3.5. Neurologic disturbances
The first reports on N2O-induced neuropathy were af-
ter recreational use. It was described after recreational use by two dentists and a hospital technician in 1978 [95]. It was soon followed up by a report on 15 patients of which 4 were dentists [96]. Some of them had occupational prolonged exposure to N2O, but also used it recreationally. Treatment with vitamin B12 resolved the problems. Chronic exposure to low concentrations of N2O in health care wor-
kers have resulted in neuropathies [97, 98, 99, 100, 101]. Such neuropathies are thus a major problem in the recre-

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child had vitamin B12 deficiency, the mother being a strict vegetarian.

Onset of subacute combined degeneration affecting the brain and spinal cord is a well documented event when individuals with low body stores of vitamin B12 are exposed to N2O. Nitrous oxide may also prove toxic in certain rare congenital disorders encountered in pediatric practice [131]. The child in this last case died 130 days of age, 46 days postoperatively and showed to have MTHFR deficiency, a rare autosomal recessive disorder.

3.6. Hematological disturbances

In the 1950’s received patients with tetanus N2O for prolonged periods to secure sedation and analgesia [10]. Nitrous oxide adminstration was the treatment of choice for tetanus [11]. Another study demonstrated that oral nitrous oxide administration was associated with marked hypothermia after 24 hours exposure in patients [12]. After several days exposure, complete bone marrow failure is expected. However, patients deficient in vitamin B12 and substrates for methionine synthesis are at potential risk even with short exposure. Occasional exposure to N2O is reported to cause bone marrow depression, reproductive disturbances, etc [14, 143, 144, 145].

3.7. Malformation and DNA disturbances

Exposure to N2O can also cause congenital anomalies. Tetrahydrofolate is involved in thymidine synthesis and DNA production. After several hours of N2O anesthesia, activity levels of methionine synthetase are very low and thus decrease tetrahydrofolate formation. The inhibition of methionine-synthetase thus can also results in interference with DNA synthesis in both leukocytes and erythrocytes [146]. Patients with sub-clinical B12 deficiency, because of illness, pernicious anemia, or nutritional deficiency, and patients with methylene-tetrahydrofolate-reductase deficiency are especially at risk [147]. Preoperative B12 followed by folate supplementation is recommended in such patients or N2O should be totally avoided.

3.8. Cardio-vascular disorders

It has been documented through a series of clinical studies that nitrous oxide administration is associated with post-operative cardiac problems. In 2015 were two cases of massive hyperhomocysteinemia after prolonged intermittent inhalation of 50 % N2O in the treatment of refractory pain reported [148]. Homocysteine has been associated with a high rate of cardiac problems [149] and cerebrovascular diseases [150]. Myocardial infarction and ST-elevation in the electrocardiogram has been demonstrated in recreational use of N2O with increase in homocysteine [151]. It leads to increased postoperative mortality [152]. This postoperative increased homocysteine and higher incidence of myocardial ischemia was confirmed in patients in a study in 2000 [153].

4. Neurotoxicity of nitrous oxide

The effect of N2O, and other volatile anesthetics, on the developing infant brain has become perhaps the most contentious area of current pediatric anesthesia discussion [154]. N2O is an NMDA antagonist and thus may have an effect on neuroplasticity and synaptogenesis in the developing brain. Evidence is cumulating that N2O has neurotoxic effects when administered during pregnancy or to children at young age [155]. Also in elderly these effects are expected to occur. Proof has been obtained from rat and non-human primate studies. Rats exposed to N2O in combination with other clinical anesthetics during the period of brain development have a consistent, excessive increase in apoptosis in various brain regions, most notably the retrosplenial cortex and thalamus [156]. Long term impairment of cognitive function in rats is described as result of neurotoxicity [157, 158]. N2O exacerbated the nervous system injury caused by isoflurane [159]. In this study in non-human primates was there widespread apoptosis in the temporal gyrus, hippocampus and frontal cortex, with evidence of both necrotic and apoptotic cell death occurring. Human demonstrated in utero or perinatal exposure to N2O a correlation with short term neurological problems such as resistance to smiles and increased muscle tone [160]. However, human studies are sparse and the results not equivocal, thus further exploration is needed. However, the large number of animal studies without any doubt proof the neurotoxic effects of anesthetics including N2O.

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