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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 (N_2O) 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 N_2O. Since the 1990's are there indications that N_2O administration in children during the period of brain development and in elderly persons has neurotoxic effects. This lead to the conclusion of many that N_2O should no longer be used in medicine. However, other physicians have the opinion that there is no reason to stop the use of N_2O.

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

Закись азота (N_2O) 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 мегалобластическая анемия. Постепенно все большее 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 (N_2O) 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 N_2O.This translates in the chemical reaction:

$$NH_4NO_3 \rightarrow N_2O + 2H_2O.$$

In 1793 experimented the British chemist Sir Humphrey Davy (1778–1829) with N_2O at 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 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 N_2O under the restriction that they had to write down the experienced effect of N_2O. Because of this and other experiences indicated Davy already the possible use in anesthesia.

In 1823 was N_2O-gas liquified by the British physicist-chemist Michael Faraday (1791–1897). 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 under nitrous oxide. That failure was probably because too short an administration of N_2O, and because of its only weak analgesic effect. At the same time came chloroform and ether in view as anesthetics. They had a stronger effect and this together with the disappointing effect of N_2O prevented the further medical use of N_2O. However, in dentistry remained N_2O widely used. The use of N_2O for tooth extraction became so popular that dentists advertised with it in the newspapers and on billboards. In 1864 started Samuel Lee Rymer (1832–1909), dentist in London, using nitrous oxide [1]. The Austrian physician Hermann Theodor Hillischer (1850-1926) can be regarded as the one introducing N_2O in 1886 in dentistry in Austria [2]. The Russian physician Stanislav Klikovich (Klikowitsch, 1853–1910) studied in 1881 mixtures of 80 % N_2O and oxygen use for painful medical manipulations. He was the first to use it in labour without loss of conscious- ness or risk of hypoxia. Klikovich recorded detailed observations on 25 women in labour to whom he had given the nitrous oxide-oxygen mixture [3, 4]. In animal studies did he confirm that nitrous oxide did not chemically combine with hemoglobin, but existed in simple solution in the plasma.

In 1886 published Dudley Wilmot Buxton (1855–1931), British physician-anesthetist his lecture 'On the physiological action of nitrous oxide' for the Odontological Society of Great Britain [5]. He found that N_2O was neither a true anesthetic nor a true analgesic, and that the effect is on the central nervous system.

During the 1940s began the administration of N_2O in combination with a number of other non-volatile anesthetic agents to allow for lower N_2O concentrations to be used. Since then was N_2O 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 N_2O and oxygen became used under the name Entonox. Since then millions of people have received N_2O as a so called harmless anesthetic, without awareness of its adverse effects. Until 1956 has N_2O 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, has it 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 N_2O in medicine, because other techniques and better and shorter acting other drugs became available.

N_2O nowadays is not only used in medicine, but also in other areas. In industry, N_2O is used as an oxidizer in atomic absorption spectrometry and in the manufacture of semiconductors. In the dairy industry, N_2O is used as a bacteriostatic, tasteless, odorless food processing propellant. N_2O is also injected into the air intake of car engines by racing enthusiasts to boost horsepower. N_2O is also used to prepare divers for deep dives 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 N_2O 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 N_2O possibly acts on a variety of such receptors. Currently is it indeed known that there are various mechanisms involved in the effect of N_2O. A direct modulation of a broad range of ligand-gated ion channels of N_2O has been demonstrated. N_2O showed to have an inhibitory action at N-methyl-D-aspartate (NMDA) glutamate receptors, while it has a stimulatory activity at dopaminergic, α_1 and α_2 adrenergic and opioid receptors. It further moderately blocks β_2-subunit-containing nicotinic acetylcholine channels, it almost insignificantly inhibits AMPA, kainate, $GABA_C$, and 5-HT3 receptors, and slightly potentiates $GABA_A$ and glycine receptors [6]. It has also been shown to activate two-pore-domaine K^+channels. In addition to its effects on ion channels, N_2O 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 N_2O.

The analgesic effect of N_2O is much stronger then its anesthetic effect. Nitrous oxide activates supraspinal opioid receptors. It was Raymond Quock 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, 9]. The analgesic effect is inhibited by Naloxone and similar compounds [10, 11]. The μ- and κ-opioid receptor are likely the places where N_2O acts [12]. In a study were μ-receptors competitively inhibited by N2O while -receptors were non-competitively bound [13]. A study where it was used as analgesic for insertion of intrauterine 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 euphoriant effects are likely caused predominantly or fully via inhibition of NMDA receptors [16]. NMDA receptors are excitatory receptors in the body which respond to the endogenous agonist glutamate. NMDA antagonists are known to have both protective and toxic effects depending on their activation. The intervention of N_2O with the NMDA receptors has powerful consequences, including the interruption of pain signals between body and brain, the mechanism by which these so-called 'dissociative' anesthetics achieve their effects; however, their onset, or use at sub-anesthetic doses, also produces a marked alteration of consciousness: the sensation that, in various ways, the mind is being unplugged from its habitual relations with the body, and entering into a

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 N_2O appears is initiated by stimulated neuronal release of endogenous opioid peptides, with subsequent activation of opioid receptors and descending GABA and noradrenergic pathways that modulate nociceptive processing at the spinal level [17]. The anxiolytic effect of N_2O involves activation of the $GABA_A$ receptor through the benzodiazepine binding site, although whether N_2O 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 enzymes, NOS, soluble guanylyl cyclase, and PKG. The anesthetic effect of N_2O appears to be caused by 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 aplastic anemia or neurologic findings similar to those of megaloblastic anemia and B12 deficiency [18, 19, 20, 21, 22]. It occurred after relatively long administrations for anesthesia. N_2O 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 was it concluded that N_2O can lead to many adverse effects i.e. hypoxia, increase in volume and pressure in gas filled body spaces, inactivation of vitamin B12, hematological disorders, immune disorders, necrologic disorders, spontaneous abortion, fertility problems, and more [26]. Also immunological problems (decreased leukocyte count, decreased leukocyte motility and chemotaxis, megaloblastic anaemia), liver problems, kidney problems, malignancy and miscellaneous cytotoxicity are described [27, 28]. Many of these adverse effects result from the irreversible inhibition of vitamin B12 by N_2O inhibition of methionine synthase, folate metabolism, and deoxyribonucleic acid synthesis is the result [29, 30, 31]. N_2O also depresses chemotactic migration by neutrophils and monocytes, apparently by interfering with microtubules [32, 33]. Increase in homocysteine concentration is another effect which may lead to increased myocardial infarction [34]. In 2017 was an extensive study published which clearly demonstrated that postoperative adverse effects such as postoperative fever, wound infection, pneumonia, pulmonary atelectasis, and severe nausea or vomiting decreased when nitrous oxide was avoided [35]. Endothelial function was impaired after surgery in patients with cardiovascular disease, but seemingly only in those exposed to nitrous oxide [36]. The duration of nitrous oxide exposure strongly correlated with the extent of endothelial dysfunction. It could be explained by the observed increase in homocysteine and a reduction in L-arginine and L-citrulline postoperatively. Despite all adverse effects is N_2O still used in many hospitals for sedation during labor and for sedation of children; frequently is it then administered without the presence of an anesthesiologist and without scavenging the waste gases.

3.1. Hypoxia and asphyxia disorders

It became known early after its introduction that the analgesic and hypnotic affects of N_2O is weak and that 100 % is needed to obtain anesthesia [37]. This of course conflicts with oxygen uptake and can cause hypoxia and even asphyxia. When the necessary 100 % N_2O is administered can hypo easily occur. In 1865 demonstrated the American dentist Zacheus Rogers (1842–1911) the use of vitalized air (N_2O) in dentistry. He reported that a mixture with 33 % oxygen was far more pleasant then 100 % N_2O. 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 N_2O to avoid hypoxia and make anesthesia safer [38]. In anesthesia is 70 % N_2O and 30 % oxygen the usual concentration administered, in sedation 50 % N_2O and 50 % oxygen.

3.2. 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 airways (LMA) can in this way increase significantly during prolonged administration of N_2O [41, 42, 43]. This may lead to local ischemia and mucosal damage. However, even tracheal rupture has been reported in two patients [44]. Damage from cuff expansion of laryngeal mask devices has also been published [45, 46, 47, 48, 49]. The diffusion is larger in silicone based tubes and laryngeal mask airways than in PVC based tubes and LMA's. Pressure increases can also occur in the middle ear or facial sinuses, the eye injected with air or sulfur hexafluoride, the ventricles of the brain when air is injected for example in pneumoencephalography. It can also cause damage to the eye from increase in pressure [50, 51, 52, 53, 54, 55]. This also occurs in cases of air embolism, expanding its size [56, 57]. It may also expand the volume of gas containing bowels [58]. The expansion becomes important when bowel obstruction is already present and the bowel contains large volumes (in excess of a liter) of gas. Closure of the abdomen becomes difficult, and the pressure of the abdominal contents upon the diaphragm may compromise ventilation.

The rapid exit of N_2O 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 been documented only when high concentrations (70 %) have been delivered by full mask or by endotracheal tube. Nitrous oxide predisposes the patient to atelectasis in isolated alveoli.

3.3. Inactivation of vitamin B12

In 1967–1968 was it found by biochemists that N_2O inactivates cobalamin (vitamin B12) by oxidation [61, 62]. This result was not appreciated in the medical community where it was only recognized in 1978 [63]. In 1982 was it demonstrated in patients' liver biopsies after exposure to 50–70 % N_2O 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 activated form S-adenosyl-methionine in hundreds of biologic 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 folinic 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 glutamate binding site on NMDA receptors, having an effect opposed to N_2O. While this might suggest that N_2O may counteract homocysteine excitotoxicity, in reality is N_2O cleared from the system very quickly following cessation of anesthesia, while homocysteine is known to stay elevated in humans serum for days. In adolescents, homocysteine levels return to baseline between 12 and 24 h [66], while in adults this post-exposure increase is still high at 24 h [67] and continued elevation has been noted for up to one week [68, 69]. Certain patient groups may be particularly susceptible to reduced methionine synthase activity, including those deficient in cobalamin. This occurs in patients with pernicious anemia or ileal disease, alcoholics, the elderly, and the malnourished [70]. The duration of administration and concentration of N_2O are important factors in the inactivation of vitamin B12 [71]. The authors found that in rats 50 % N_2O exposure decreased methionine synthase activity within 30 min, and the activity was virtually undetectable after 6 h. Since N_2O readily passes the placenta is also the fetus affected. In 1985 was it for the first time demonstrated that an adverse influence of N_2O on vitamin B12 metabolism and DNA synthesis exists also in humans [72]. Exposing rats to N_2O for 2 hours revealed in a 50 % reduction of methionine synthetase. Mice, pigs, and rats exposed to N_2O 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 posterior and lateral columns of the spinal cord, because it is essential in the production and maintenance of myeline. Clinical symptoms include sensory neuropathy, myelopathy, and encephalopathy; they can occur within days or weeks after exposure to N_2O anesthesia in people with subclinical vitamin B12 deficiency. In humans, the mean half-time for hepatic methionine synthase inactivation by 1 atmosphere N_2O is approximately 1 hour (or 0.5 atmospheres for 2 hours), with less than 20 % residual activity after 2 atmosphere-hours of exposure [78]. However, others found 50 % reduction after exposure for 40 minutes to 50 % N_2O [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 administration. A second exposure during this interval may be especially harmful because it prolongs the period of diminished methionine synthase activity. Repeated use of N_2O depletes the body stores of vitamins B12 even in healthy people. Health care workers are frequently exposed to N_2O and may develop all adverse effects of it [80, 81]. Also non-health care workers exposed to N_2O can experience adverse effects [82]. Preoperative treatment with folinic 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 methionine synthase concentration due to N_2O causes lasting impairment of memory [84]. Others demonstrated that exposure to N_2O 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 conversion disorder with myeloneuropathy was published [91]. N_2O 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 was it 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 after inhalation of 40 % nitrous oxide had ceased [94].

3.5. Neurologic disturbances

The first reports on N_2O-induced neuropathy were after 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 14 were dentists [96]. Some of them had occupational prolonged exposure to N_2O, but also used it recreationally. Treatment with vitamin B12 resolved the problems. Chronic exposure to low concentrations of N_2O in health care workers have resulted in neuropathies [97, 98, 99, 100, 101]. Such neuropathies are thus a major problem in the recreational and less frequently also after anesthesia [102]. Numbness, tingling, ataxia and/or muscle weakness, and impotence are frequently described [103, 104]. Animal studies have confirmed these effects [105, 106]. Vitamin B12-deficient patients are more at risk to develop neurologic disorders from N_2O toxicity [107]. Consequently is it important to replace vitamin B12 in the malnourished before nitrous oxide anesthesia administration. However it is difficult to diagnose the deficiency unless clinical symptoms are present.

For subjects with good body stores of cobalamin is methionine synthetase inhibition unimportant, but no one using this agent should remain unaware of the potentially devastating complications in the nervous system of using N_2O in subjects who are of borderline or deficient vitamin B12 status. Several investigators have reported the development of myelopathy and cord degeneration 2 to 6 weeks after a single nitrous oxide anesthesia induced for a variety of surgical procedures [108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119]. Some of them had an undetected vitamin B12 deficiency. The myelopathy most frequently occurs in the lower cervical and upper thoracic regions. Vitamin B12 or folate deficiency without exposure to N_2O can also lead to sub-acute combined degeneration of the cord, presenting as limb weakness, numbness and tingling with imbalance and other neurologic disorders [120, 121].

Also in recreational use of N_2O does myelopathy occur [122, 123, 124, 125, 126]. Most of these patients were found to have underlying vitamin B12 deficiency that was unknown at the time of the N_2O use. Then one or two exposures are sufficient to result in myelopathy [127]. Awareness of this process is critical since approximately 14 % of the population have a vitamin B12 deficiency. Most symptoms improve, but do not resolve completely upon administration of vitamin B12 and methionine [128]. Peripheral nerve biopsies in patients with deficiencies show morphologic changes, i.e. degenerated nerve fibers, myelin splitting and formation of intra-myelinic vacuoles containing myelin debris [129]. Also neurophysiological changes such as delayed conduction velocity, can be observed. For example, a 6-month-old girl developed hypotonia and collapsed with metabolic acidosis, reduced serum cobalamin, and diffuse cerebral atrophy after a short nitrous oxide anesthesia [130]. Both mother and

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 N_2O. 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 N_2O for prolonged periods to secure sedation and analgesia [132]. They developed bone marrow depression and granulocytopenia. Two patients died from aplastic anemia. N_2O is known to impair neutrophil and monocyte chemotaxis. In 1963 was it found that N2O in rats has a depressant effect on hemopoiesis [133]. The production of white blood cells was decreased. In 1981 demonstrated a study that short exposure to N_2O did not cause bone marrow changes, but that longer exposure, i.e. more than 12 hours, did [134]. Administration of folic acid prevented these changes. In 1981 was a relationship between hematologic and neurology disturbances with chronic N_2O exposure demonstrated in a survey amongst 18000 dentists and 18000 dental assistants [135]. Also others found that megaloblastic changes in bone marrow are present following exposure to anesthetic N_2O concentrations for 24 hours, and that agranulocytosis is apparent after 4 days of exposure to it [136, 137]. However, such changes were by others found to exist already after an exposure during 2 hours and less [138]. Especially older patients are prone to megaloblastic anemia, because 20 % of them have already methionine synthase deficiency from malnutrition [139]. Leucopenia results from nitrous oxide administration [140]. Another study found that mild megaloblastic changes (associated with B12 deficiency) are present after 12 hours, and are marked after 24 hours exposure in patients [141]. After several days exposure, complete bone marrow failure is expected. However, patients deficient in vitamin B12 and substrates for methionine synthase, are at potential risk even with short exposure. Occupational exposure to N_2O is reported to cause bone marrow depression, reproductive disturbances, etc [142, 143, 144, 145].

3.7. Malformation and DNA disturbances

Exposure to N_2O can also cause congenital anomalies. Tetrahydrofolate is involved in thymidine synthesis and DNA production. After several hours of N_2O 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 N_2O should in them be 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 % N_2O 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 N_2O 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 N_2O, and other volatile anesthetics, on the developing infant brain has become perhaps the most contentious area of current pediatric anesthesia discussion [154]. N_2O is an NMDA antagonist and thus may have an effect on neuroplasticity and synaptogenesis in the developing brain. Evidence is cumulating that N_2O 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 N_2O 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]. N_2O 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 N_2O 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 N_2O.

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