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Anesthetic gases as an occupational hazard — A review

by Christer Edling, MD

Inhalation anesthesia was first used in 1842, when an American physician administered diethyl ether (common ether) to a patient. Since then many different compounds have been used as inhalation anesthetic agents, and many of these have later been utilized as industrial solvents, eg, trichloroethylene and chloroform. The first report to indicate that people working in operating rooms could become ill as a consequence of exposure to anesthetic gases, especially chloroform, came at the end of the 19th century. Nevertheless, the physical properties of anesthetic agents have attracted the most interest. Especially questions concerning volatility, flammability and dangers of explosion have come to the fore. Thus systems for the elimination of anesthetic gases from operating rooms were described at the beginning of the 20th century, and the anesthetic compounds have become less explosive and flammable through the introduction of halogenated anesthetic agents in the mid 1950s. During the last decade, however, interest has more and more been focused on the health hazards for operating room personnel.

Initially, acute subjective effects on operating room personnel were pointed out, eg, headache and tiredness. However, there is also information on organ damage. As early as 1922 a case report appeared of an anesthetist with nephritis, and in 1949 a German case report concerned personnel who had been exposed to ether for 4 to 14 a and showed electrocardiographic evidence of myocardial damage.

This review elucidates the studied side effects of long-term exposure.

Teratogenicity and mutagenicity

Bacterial tests

The studies on the mutagenicity of anesthetic agents in bacterial systems are few and contradictory. Halothane, methoxyflurane, enflurane, trichloroethylene, and isoflurane have been tested, but no evidence of mutagenicity was found (3, 4, 67). On the other hand, fluoxene was mutagenic in the same test system (4), and another study has reported trichloroethylene as a mutagen (34). The urine of anesthesiologists exposed to halothane induced mutations in the conventional Ames assay (48), and halothane has been described as an “insufficiently positive mutagen” (36).
Animal tests

The results of many animal studies have been published concerning the teratogenic effect of nitrous oxide and halogenated anesthetic agents. A review of these reports is given in the criteria document on waste anesthetic gases and vapors (51) that has been published by the US National Institute for Occupational Safety and Health (NIOSH). In most of the studies very high exposure levels were used, and it is therefore difficult to compare the results of the animal experiments with what could be expected from the far lower exposure levels in operating rooms. In a recently published study (66), however, pregnant rats exposed day and night for 19 d to a mixture of 0.5 % nitrous oxide in air, ie, about the same level of pollution as in operating rooms, showed a much greater percentage of damage to the fetus, ie, fetal resorption and skeletal anomalies, in comparison with nonexposed rats. In another study (54) an animal model was used to investigate the fetal toxicity of halothane, nitrous oxide, and methoxyflurane. High subanesthetic concentrations of all the inhalation anesthetics could cause fetal growth retardation, but this phenomenon was unaccompanied by significant fetal loss. It was concluded that the study did not implicate any specific inhalation anesthetic agent in fetal toxicity, and that the effects of additional factors, such as stress, must be considered.

Epidemiology

The first epidemiologic study of spontaneous abortion and malformations was published in 1967 when Vaisman (64) reported a Russian study on 303 (193 men and 110 women) anesthesiologists. The author noted that among 31 earlier pregnant anesthesiologists, aged 24—38 a, one pregnancy in three had ended in spontaneous abortion, two women gave birth prematurely, and in one case the child had congenital malformations. The anesthetic gas in use during the period of exposure was mostly ether, but even nitrous oxide and halothane had been used.

This report was later followed by a Danish study (1) in which 578 nurses of anesthetic departments and 174 female and male anesthesiasts were questioned by means of questionnaires. A total of 212 pregnancies before and 392 during exposure to anesthetic gases was reported. The abortion frequency was significantly higher for the exposed women (20 %) in comparison with the nonexposed ones (10 %). In this study the authors even reported a higher frequency of spontaneous abortions among nonexposed women whose husbands worked as anesthesiologists. Similar results were reported in an American study from 1975 (17), in which wives of exposed dentists had a higher frequency of spontaneous abortion in comparison with nonexposed referents. In two English questionnaire surveys (42, 43), in which 1,431 male and 849 female anesthesiologists answered, the results indicated a higher rate of spontaneous abortion among exposed women, whereas the husbands' exposure did not seem to influence the outcome of pregnancy. Findings of a higher frequency of spontaneous abortion among exposed women have been reported in several studies from many countries, eg, Sweden (31), Finland (56), West Germany (29), and Czechoslovakia (51). In a recently published English study on anesthesiasts' health problems, including 10 % of all anesthesiasts in England and Wales, the author reported a higher frequency of spontaneous abortion among female anesthesiasts than among nonexposed women (63).

In some of the studies, eg, those by Cohen et al (16), Knill-Jones et al (43) and Göt et al (31), a higher risk of malformations among children born by women exposed to anesthetic gases during pregnancy was also shown. In the study by Göt and his co-workers, a difference was even found between smokers and nonsmokers in that nonsmokers more often bore malformed children, whereas pregnancies among smoking women more often ended in spontaneous abortion, the possibilities of malformations occurring thereby being diminished. In his study of English anesthesiasts (63), Tomlin reported an increased frequency of malformations, especially in the central nervous and musculoskeletal systems. Paraoh et al (53) surveyed the obstetric
history of 5,700 women physicians in England and Wales; conceptions that occurred when the mother was in an anesthetic appointment resulted in smaller babies, higher stillbirth rates, and more congenital malformations of the cardiovascular system than those of other women physicians. There was, however, no significant difference in the spontaneous abortion rate between the two groups. A Swedish study (5) reported the pregnancy outcome, i.e., perinatal mortality and congenital malformations, for women working in medical occupations before giving birth. The outcome of pregnancies was checked with the aid of existing central registers and compared with the outcome of pregnancies for the whole country. There was no difference in the observed and expected number of perinatal mortality and congenital malformations among women working in anesthesia and operation departments.

Carcinogenicity

During the last several years the possibility of a carcinogenic effect of anesthetic gases has attracted some attention. The anxiety about this effect is not totally unjustified, since there are many structural similarities between some known human carcinogens (i.e., dibromoethane, dichloroethylene, bischloromethyl ether, and chloromethyl methyl ether) and several of the inhalation anesthetic agents now in use. Besides, anesthetic compounds can be transformed into reactive metabolites which can combine with tissue macromolecules (15) and thereby turn into chemical carcinogens (7).

Animal tests

Studies on rats and mice have demonstrated that at least some of the volatile anesthetic agents are capable of inducing cancer. In an early experiment, Eschenbrenner (27) induced hepatoma by giving mice very high doses of chloroform perorally. In 1976 the National Cancer Institute (NCI) (49) reported animal tests in which rats had been given chloroform perorally in doses of one-fifth to one-tenth of those of Eschenbrenner. A significant increase in kidney tumors, as well as hepatocellular carcinomas, was observed. The NCI has even made animal studies regarding the carcinogenicity of trichloroethylene. By gastric intubation trichloroethylene was administered to rats; the result was an increase in hepatocellular carcinomas (50). However, in all these three studies, the methods of exposure were quite unusual when compared with occupational exposure in an operating room. Therefore, no conclusion can be drawn on the basis of these studies, except that the investigations indicate that the tested substances have some carcinogenic potential.

As for halogenated anesthetic gases, an animal experiment was made by Corbett (18) in which pulmonary and hepatic neoplasms were induced in the offspring of mice by repeated exposure of the mother during pregnancy and of the offspring after delivery to subanesthetic concentrations of isoflurane (0.1—0.5%) isoflurane). In another study (26), mice were exposed, both in utero during the last half of pregnancy and after delivery, to low doses of either enflurane, isoflurane, halothane, methoxyflurane, or nitrous oxide. The result did not confirm the suggestion that isoflurane is a hepatocarcinogen, nor did the data suggest that inhaled anesthetics currently in use pose a significant threat of carcinogenicity.

Coate et al (14) studied the effects of prolonged exposure to low-concentration combinations of halothane and nitrous oxide on tumor incidence. Rats were exposed to filtered air, 1 ppm of halothane and 50 ppm of nitrous oxide or 10 ppm of halothane and 500 ppm of nitrous oxide. Histologic evaluation of the reticuloendothelial system and of other major organs did not reveal any enhancement of the spontaneous tumor rate or any unusual neoplasms.

Epidemiology

In a retrospective cohort study (9) the mortality among anesthesiologists, in 1947—1966, was studied. An increased frequency of malignant diseases in the
lymphoid and reticuloendothelial system was reported among the 441 deceased persons (9). A later follow-up of the mortality during 1967—1971 did not, however, reveal any increase in deaths from tumors (10). In another large American study, in which morbidity was followed in a questionnaire survey of 73,496 persons, it was found that women, but not men, exposed to anesthetic gases had a higher frequency of cancer, especially leukemia and lymphoma (16). In other American studies (19, 20) the incidence of malignant diseases among 525 anesthetic nurses was followed. Excluding skin cancer, a higher incidence of unusual tumors, such as malignant lymphoma, leiomyosarcoma, hepatocellular carcinoma, and cancer of the pancreas, was found. Furthermore, the occurrence of cancer among children born by anesthetic nurses was studied, and for them also a higher cancer incidence was found. The same findings, cancer among children, were also observed by Tomlin (63). These data could indicate that anesthetic gases can act as a transplacental chemical carcinogen, as has been reported for some other substances in man, ie, diethylbestrol (37), barbiturates (32), chlorinated pesticides (39), and smoking (52). A few English studies (24, 43, 53) have not disclosed any increase in cancer among anesthesiologists, but in a newly published investigation from the same country a higher cancer risk among this group is claimed (63). It must also be mentioned that both a Swedish (2) and Finnish (62) cohort study on industrial exposure to trichloroethylene showed no increased cancer incidence.

available on the effects on operating room personnel. There are, however, case reports of liver damage among patients anesthesized with halothane and a report on a temporary increase of liver transaminases among operating personnel working with halothane (30). There are also case reports on icterus and liver cirrhosis among anesthetists exposed to halothane (6, 41). In some of the larger epidemiologic studies made in America (16, 17) and Czechoslovakia (51), an increased frequency of liver disease among anesthesiologists was observed. In England Spence & Knill-Jones (80) reported significantly more liver disease among anesthesiologists than among other hospital personnel.

Kidneys

In animal experiments kidney damage has been reported after exposure to low levels (100—500 ppm) of halothane (13). An effect on man has been reported on several occasions, where side effects have been noticed in patients anesthetized with methoxyflurane (21, 22). In 1968 there was a retrospective cohort study made among anesthetic personnel; it reported an increase in chronic kidney disease (9). In the earlier mentioned studies by Cohen et al (16) and Uhlirova & Pokorny (51), there was a higher frequency of kidney disease among exposed persons, especially women. In a Swedish report (23) a moderate and temporary effect on kidney function was shown among patients, as well as personnel, exposed to methoxyflurane.

Bone marrow

Animal studies, as well as clinical experience, on the effect of prolonged exposure to high concentrations of nitrous oxide have shown that leukopenia may be induced (33, 45). This effect has been used in the treatment of chronic and acute myeloid leukemia (25). However, because of the rapid recovery of marrow, it has been ineffective as a choice of treatment for leukemia (68). As to the effect on exposed personnel, there are no reports concerning bone marrow depression.

Other organ effects

Liver

In many animal experiments liver damage has been reported after exposure to high doses of halothane and methoxyflurane (51), and also after long-term exposure to subanesthetic concentrations of halothane, isoflurane, and diethyl ether (61). On the other hand, there are very few reports
Central nervous system

Many of the industrial solvents now in use have earlier been used as anesthetic agents. Solvents, as well as anesthetic agents, are fat-soluble, which is also one of the conditions for the narcotic effects. Besides, anesthetic gases can form toxic metabolites in the same manner as many solvents; these metabolites react on the cellular level and can induce cell damage there. The chronic damage caused by solvents has been studied to a great extent during the last 10 years, and many studies have shown effects on the central nervous system as a consequence of long-term exposure to solvents. Today there are no studies on the chronic central nervous effects on anesthetic personnel exposed for many years to anesthetic gases. However, animal and human experiments indicate that exposure to anesthetic gases does affect the central nervous system (CNS).

Animal experiments have shown CNS damage in rats after exposure to halothane in concentrations of 8–12 ppm for 8 h a day 5 days a week. In a laboratory study, 100 healthy male students were examined. They were subdivided into five groups with 20 persons in each. The groups were exposed to different combinations of anesthetic agents, i.e., from 25 ppm of nitrous oxide and 0.5 ppm of halothane up to 500 ppm of nitrous oxide and 10 ppm of halothane. These concentrations were supposed to be in agreement with the levels very often existing in operating rooms during operations. The results showed that as little as 50 ppm of nitrous oxide led to an impairment of performance of about 5%. When 1 ppm of halothane was added, the impairment of performance was about 10%, when measured by different psychological functional tests.

In another study, where the behavioral toxicity of anesthetic gases on operating room personnel was studied, halothane levels of 1–3.9 ppm and nitrous oxide concentrations of about 0–176 ppm were registered. The exposed group was compared with a reference group, but there was no evidence of any acute reversible disturbance, measured by psychometric tests, but the possibility of subtle but irreversible deficits could not be ruled out.

In Sweden, Gamberale et al published a study in which they measured reaction time and perceptive speed among nurses who were exposed to anesthetic gases in their daily work. The results were compared with those of 20 nurses with intensive care duties but without exposure to anesthetic gases. No measurable impairment in the reaction time of the anesthetic personnel was observed in comparison to that of intensive care personnel. In one of the tests of reaction time, however, the result showed that the range of the individual reaction times among the anesthetic nurses was greater than that of the reference group.

In a study from Gothenburg, Sweden, 32 anesthetic nurses were compared with a nonexposed matched reference group. The study comprised a psychological test battery, a questionnaire measuring feelings, a questionnaire measuring symptoms, and, finally, a purely medical phase. For only two of the 18 psychological test variables were the anesthetic nurses significantly inferior to the reference group. Moreover, there was only one subjective symptom that showed a significant difference between the groups, namely, pricking and numbness in any part of the body. However, in the psychological test and in regard to symptoms, there was a clear-cut tendency towards poorer test results and more symptoms among the anesthetic nurses than among the referents. The authors also tried to divide the exposed groups according to high- and low-level exposure, years in exposed work being used as the measure. When the level of exposure was related to the test results, they found a tendency towards poorer performance in the high exposure group when it was compared with the low exposure one.

In Finland, Korttila et al looked into the driving skills of operating room nurses after occupational exposure to halothane (0–43.7 ppm) and nitrous oxide (100–1,200 ppm). The driving skills of 19 nurses were measured and compared to those of 11 younger nurses working in the wards of the same hospital but with no exposure
Peripheral nervous system

In accordance with the earlier mentioned similarities between industrial solvents and anesthetic gases now in use, it is not surprising to find that nitrous oxide can possibly cause neuropathy. Layzer et al (47) reported a disabling peripheral neuropathy in three health workers who habitually abused nitrous oxide. Nerve conduction studies suggested an axonal rather than demyelinative neuropathy. The neurologic disorder improved slowly when the patients abstained from further nitrous oxide abuse (47).

In another study Layzer (46) reported a neurologic disorder in 15 patients after prolonged exposure to nitrous oxide. Thirteen of the patients had abused nitrous oxide to some extent for periods ranging from three months to several years, but two patients were exposed to nitrous oxide only professionally, as dentists, during work in poorly ventilated offices. Neurologic examinations showed sensorimotor polynuropathy and a picture similar to that of subacute combined degeneration of the spinal cord. The author claimed that it is possible that nitrous oxide interferes with the action of vitamin B₁₂ in the nervous system.

There is also a report (57) of toxic polynuropathy, in a 23-year-old woman, after excessive intentional inhalation of nitrous oxide. The chronology of the patient's abuse correlated clearly with two episodes of recurrent polynuropathy, primally involving the peripheral nerves, although some signs suggested a possible effect on the cerebellum or its connections. Biopsy of the sural nerve showed axonal degeneration. The patient had inhaled nitrous oxide, dispensed from cartridges, through a canister normally used for whipped cream. Gas chromatographic analysis revealed exposure to, besides nitrous oxide, 26 other compounds. Three of these, trichloroethylene, toluene and phenol, are known neurotoxins.

Information about exposure

In the existing epidemiologic studies measures of exposure have rarely been given, but other references (30, 31, 40, 44, 51) indicate that the levels of anesthetic gases in operating rooms are highly variable. Usually the levels of halothane are about 1—70 ppm and those of nitrous oxide 400—3,000 ppm in older operating rooms with poor general ventilation. However, even in new facilities, there can be high levels, the tendency towards leakage being especially influenced by the anesthetic technique used, i.e., face mask or intubation. This great variation in exposure has made it very difficult to settle on a safe exposure level for anesthetic gases. Based on epidemiologic studies, animal experiments, exposure measurements, and experimental studies, especially that of Bruce & Bach (8), NIOSH has concluded that a safe level of exposure to the halogenated agents cannot be defined, but it recommends that exposure be controlled to levels around 2 ppm and that the permissible level of exposure to nitrous oxide alone should be 25 ppm during the period of administration (51). It must, however, be stressed that today there are no settled threshold limit values (TLVs) for waste anesthetic gases in the United States. In Sweden a TLV for halothane of 5 ppm has been in effect since 1979, and one for nitrous oxide is under preparation. In Denmark the Labor Inspection Service has suggested a TLV of 1 ppm for halothane and 25 ppm for nitrous oxide. In Finland and Norway the subject is under consideration, but no information is available.

Summary

During the last 10 years, several studies have shown different health hazards for operating room personnel. Even if there are methodological weaknesses in many of the epidemiologic studies, such as low response rates or a lack of or poor definition of reference groups or no information on the anesthetic agents used or the environmental concentrations of the gases present, many studies indicate a higher risk for spontaneous abortion among women ex-
posed to anesthetic gases. Even very critical reviews (60, 65) conclude that available data provide reasonably convincing evidence of a moderate increase in the risk of spontaneous abortion among exposed females. Less agreement is found in the information on the increased risk for spontaneous abortion among women whose husbands have been exposed to anesthetic gases or on the increased risk of exposed women having malformed children. The same discrepancy applies to the reports on liver and kidney disease and the risk of cancer. However, the reports on a higher risk of cancer are worth attention in that the urine of anesthesiologists has been found to be mutagenic and there are structural similarities between some known human carcinogens and several inhalation anesthetic agents. Another growing concern is the possible CNS effects of long-term exposure to waste anesthetic gases. As yet no such studies have been performed. Consequently, there is a need for epidemiologic studies on the frequency of cancer, with special emphasis on leukemia and lymphoma, and behavioral deficits.

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