Genetic damage in operating room personnel exposed to isoflurane and nitrous oxide

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Abstract

Objectives—To evaluate genetic damage as the frequency of sister chromatid exchanges and micronuclei in lymphocytes of peripheral blood of operating room personnel exposed to waste anaesthetic gases.

Methods—Occupational exposure was measured with a direct reading instrument. Venous blood samples were drawn from 10 non-smokers working in the operating room and 10 non-smoking controls (matched by age, sex, and smoking habits). Lymphocytes were cultured separately over 72 hours for each assay with standard protocols. At the end of the culture time, the cells were harvested, stained, and coded for blind scoring. The exchanges of DNA material were evaluated by counting the number of sister chromatid exchanges in 30 metaphases per probe or by counting the frequency of micronuclei in 2000 binucleated cells. Also, the mitotic and proliferative indices were measured.

Results—The operating room personnel at the hospital were exposed to an 8 hour time weighted average of 12.8 ppm nitrous oxide and 5.3 ppm isoflurane. The mean (SD) frequency of sister chromatid exchanges was significantly higher (10.2 (1.9) v 7.4 (2.4)) in exposed workers than controls ($p=0.036$) the proportion of micronuclei (micronuclei/500 binucleated cells) was also higher (8.7 (2.9) v 6.8 (2.5)), but was not significant ($p=0.10$).

Conclusion—Exposure even to trace concentrations of waste anaesthetic gases may cause dose-dependent genetic damage. Concerning the micronuclei test, no clastogenic potential could be detected after average chronic exposure to waste anaesthetic gas. However, an increased frequency of sister chromatid exchanges in human lymphocytes could be detected. Although the measured differences were low, they were comparable with smoking 11–20 cigarettes a day. Due to these findings, the increased proportion of micronuclei and rates of sister chromatid exchanges may be relevant long term and need further investigation.

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Although several efforts have been made to minimise the exposure to waste anaesthetic

gases by improving the working environment, contamination of operating room air is still unavoidable, whenever anaesthetic agents were given by inhalation.^{1,2} Whether these traces of anaesthetics are hazardous to the health of personnel or not is controversial. Recently, several independent groups suggested that there is a health risk associated with chronic occupational exposure to waste anaesthetic gases.^{3–5} These studies were mainly focused on spontaneous fetal abortions leading to the assumption that genetic damage of the fetus occurs during pregnancy. A causal factor seems to be the mutation of the DNA material due to exposure to anaesthetic gases.

One sensitive way to evaluate mutagenicity is to count the number of exchanges between two chromatids of a chromosome of cultured human lymphocytes.⁶ An increased number of such sister chromatid exchanges reflects the influence of mutagens. Another possibility is to count the number of micronuclei as a quantitative measure for both structural and numerical chromosome aberrations.⁷

Currently, the available data seem to be inconsistent. This is probably due to the fact that a dose-response relation is lacking as there are insufficient exposure measurements.

Therefore, the purpose of our study was to measure the occupational exposure to waste anaesthetic gases, to compare these values with the currently valid exposure limits (table 1), and to determine their effect on the amount of genetic damage, with the micronucleus assay and the sister chromatid exchange test in human lymphocytes.

Methods

SUBJECTS

The study was conducted after approval of the Institutional Review Board at the Animal Hospital of the University of Berlin, Germany. All veterinary surgeons ($n=11$) in the department working routinely in the operating room were asked to participate in the study. After their consent, 11 of 18 non-exposed veterinary physicians were selected to provide best possible matching for age and sex. Each subject, aware of the study hypothesis, was personally interviewed with a standardised questionnaire containing questions on drug intake, contraception, diseases during the previous 3 months, smoking, and diagnostic and therapeutic x ray exposure. After the interview, one pair had to be excluded due to concomitant illness during the study period. Finally, 10 non-smoking exposed veterinary surgeons were compared with 10 non-smoking non-exposed veterinary physicians.

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Table 1 International threshold value; current threshold values as time weighted averages (TWA) ppm; NIOSH values refer to the time of exposure during anaesthetic administration, all other countries refer to an 8 h working day TWA

	N ₂ O	Halothane	Enflurane	Isoflurane
Austria	—	5	—	—
Denmark	100	5	2	—
France	—	2	—	—
Germany	100	5	20	10
Great Britain	100	10	50	50
Italy	100	—	—	—
Sweden	100	5	10	10
Switzerland	100	5	10	10
USA-NIOSH	25	2	2	2
USA-ACGIH	50	50	75	—

DESCRIPTION OF THE WORKPLACE

The measurements were performed in an operating room with an air volume of 130 m³. Air was conditioned by a laminar flow system producing an air exchange rate of 17 air turnovers an hour without recirculation. The exhaust outlets of the anaesthetic machines of the operating room were connected to the hospital's central scavenging system with a suction flow of 45 l/min.

DATA ACQUISITION AND ANALYSIS

Time weighted averages were calculated as in previous studies and currently valid health authority regulations.^{1,2} Measurements of trace concentrations were taken every minute in the breathing zone of the surgeon by means of a direct reading instrument (Brüel and Kjaer 1301, Naerum, Denmark) over the course of an 8 hour working day for 1 week. The analysis technology was based on photoacoustic infrared spectrometry. The system was calibrated for each substance with trace gas mixtures—for example, 15.3 ppm isoflurane in pure nitrogen. The typical lower detection limit was 0.1 ppm for both anaesthetics and the accuracy was within 2% over a linear range of 0.1–1000 ppm.

The data acquisition was performed on floppy disk by the analyser. Detailed analysis was accomplished with an Apple computer system (Motorola 68040 processor, running under MacOS 7.6) by means of the SPSS 6.1 for Macintosh software.

LYMPHOCYTE MICRONUCLEUS ASSAY

Lymphocytes were isolated from 5 ml of whole blood obtained from the volunteers at the end of the week of monitoring by a Ficoll-Paque density centrifugation,⁸ and washed twice with pH 7.2 phosphate buffered saline (PBS). Micronucleated lymphocytes were measured with a modified cytokinesis block technique.⁷ Cells were cultured at 37°C for 72 hours in 5 ml chromosome medium 1A (Gibco, Vienna, Austria) that contained 10 ml/l phytohaemagglutinin. Cytochalasin B (3 µg/ml final concentration, Sigma, Vienna, Austria) was added after 44 hours of incubation. After 72 hours the cells were treated with hypotonic saline, fixed in methanol/glacial acetic acid (3:1), and harvested on slides. The slides were dried and stained for 15 minutes in 4',6-diamidino-2-phenylindole (DAPI, 5 mg/l, Serva, Heidelberg, Germany). Two thousand binucleated cells per blind sample were scored by one investigator. Micronuclei had to meet the

following criteria: (a) DAPI positive, (b) less than one third the diameter of the main nucleus, (c) in the same plane of focus, (d) the same texture as the main nucleus, (e) a smooth oval or round shape. The values were presented as the number of micronuclei per 500 binucleated cells.

SISTER CHROMATID EXCHANGE

Whole blood (0.5 ml) cultures were established in 5 ml chromosome medium 1A (Gibco), containing 50 µM 5-bromo-2'-deoxyuridine (BrdUrd, Sigma, Deisenhofen, Germany). After 70 hours demecolcine (Sigma, Deisenhofen, Germany) with a final concentration of 0.1 µg/ml was added to each culture. Two hours later the cells were washed and fixed. According to a standard protocol the cells were stained with Giemsa (Sigma, Deisenhofen, Germany) and the slides were coded by an independent investigator to provide a blinded scoring.⁹

MEASUREMENT OF THE PROLIFERATIVE RATE INDEX, MITOTIC INDEX, AND SISTER CHROMATID EXCHANGE

Cell cycle kinetics were examined by scoring the proportion of cells at M₁ (metaphase cells in the first replication cycle), M₂, and M₃. A delay in cell proliferation was indicated by a decrease in the frequency of M₂ or M₃ and a corresponding increase in M₁ replication cells, or as a decline in the proliferative rate index. The proliferative rate index was calculated according to the formula:

$$\text{proliferative rate index} = (1 \times M_1\% + 2 \times M_2\% + 3 \times M_3\%) / 100^{10}$$

The mitotic index was calculated as the proportion of metaphases among the total cell population and was estimated by counting a total of 1000 cells.¹⁰

Metaphases with few or no overlaps were selected from slides coded by an independent investigator to provide a blinded scoring. The locations of these metaphases were identified with coordinates. The frequency of sister chromatid exchanges was measured by examining 30 complete second metaphases, one sister chromatid exchange being counted when two adjacent segments of one of the chromatids in a chromosome were stained differently. The value of sister chromatid exchanges for each specimen was taken as the mean rate of sister chromatid exchanges per metaphase.

STATISTICS

Before starting the experiments, a statistical plan of the study was performed. The intention was to detect a mean (SD) difference between the groups of 2 (1.5) sister chromatid exchanges per cell. Considering the variability between people, an α error of 5%, with a two sided paired *t* test, the study population was calculated to be nine probands in each group to reach a minimum power of 90% (nQuery software for Windows 95).

After data acquisition the arithmetic means (SDs) were calculated for each group. Paired Student's *t* test (with 9 degrees of freedom) was applied to determine significant differences

Typical recording of isoflurane and nitrous oxide during one working day.

between the treated cells with $p \leq 0.05$. The power of this study calculated after it was finished was 95%.

Results

EXPOSURE ASSESSMENT

An example of a typical measurement of waste anaesthetic gas is shown in the figure. During the whole week of monitoring, 92% of the measurement time was under the NIOSH value of 25 ppm nitrous oxide, and 99% <100 ppm. Of the isoflurane values 86% were under the United States National Institute for Occupational Safety and Health (NIOSH) 2 ppm limit, and 94% <10 ppm. Due to the short duration of high exposure the overall calculated 8 hour time weighted averages were 5.3 ppm

for isoflurane and 12.3 ppm for nitrous oxide obtained from the measurements of the whole week of monitoring.

LYMPHOCYTE MICRONUCLEUS ASSAY

The number of micronucleated lymphocytes was higher in the exposed group than the non-exposed group (table 2), but the difference was not significant ($p=0.10$, 95% confidence interval (95% CI) 0.44 to 4.24). Differences were also found between subsets of exposed and non-exposed men and women. The differences were exposed men 7.8 (3.0) micronuclei/500 BNC *v* control men 5.1 (2.3) ($p=0.229$, 95% CI -2.99 to 8.36), and exposed women 9.3 (3.0) *v* control women 7.9 (2.1) ($p=0.35$, 95% CI -2.08 to 4.83).

SISTER CHROMATID EXCHANGE

There was a significant difference in the rate of sister chromatid exchanges between exposed and control workers ($p=0.036$, 95% CI 0.22 to 5.28, table 2). Differences between the men and women in subsets were also found, but were not significant. The values for the exposed men were 9.3 (2.2) *v* control men 6.8 (1.9) sister chromatid exchange/cell ($p=0.167$, 95% CI -2.26 to 8.24) and for the exposed women 10.4 (1.9) *v* control women 7.8 (2.7) ($p=0.174$, 95% CI -1.60 to 6.78).

The values for the proliferative index and mitotic index did not differ between exposed and control people (table 2).

Discussion

Several studies indicate that an occupational exposure to waste anaesthetic gases is associated with adverse effects in healthcare workers.¹¹⁻¹⁴ However, other studies could not identify a significant correlation.^{15 16} Although these studies were criticised because of the design limitations, meta-analysis identified substantial reasons of concern, even when analysis was restricted to the best available

Table 2 Demographic data and the results in the different groups

Patient No	Age (y)	Sex (n/cell)	SCE (n/500 BNC)	MN (%)	PRI (%)	MI
Exposed group:						
1	52	M	8.59	10.75	2.00	5.43
2	26	F	9.12	13.00	1.50	3.47
3	31	M	12.99	6.75	2.25	6.44
4	27	F	7.87	7.50	2.36	2.81
5	26	M	8.15	9.75	2.11	7.58
6	31	F	13.40	5.50	1.82	6.41
7	35	M	9.58	4.00	2.12	6.58
8	33	F	10.29	9.75	2.42	3.68
9	40	F	10.08	12.50	2.33	1.72
10	27	F	11.72	7.50	2.21	6.78
Mean	32.80	10.18	8.70	2.11	5.09	
SD	8.11	1.95	2.95	0.28	2.00	
Control group:						
1	51	M	6.37	6.25	2.08	4.62
2	25	F	8.35	6.00	2.27	2.99
3	30	M	5.35	7.75	1.75	3.20
4	27	F	12.03	6.50	1.91	8.70
5	27	M	5.88	3.00	1.80	2.88
6	30	F	6.39	5.75	2.16	6.00
7	38	M	9.74	3.50	2.05	3.69
8	33	F	6.62	9.25	1.75	4.58
9	41	F	4.30	9.75	2.07	2.64
10	27	F	9.28	10.25	2.15	3.85
Mean	32.90	7.43	6.80	2.00	4.32	
SD	8.18	2.36	2.47	0.18	1.85	

SCE=sister chromatid exchanges; BNC=binucleated cells; MN=micronuclei; PRI=proliferative rate index; MI=mitotic index.

data.⁴ Unfortunately, most previous epidemiological studies lack the connection between the amount of exposure and the resulting adverse health effects. Although Rowland *et al* showed the adverse effect of nitrous oxide on fertility and spontaneous abortion,^{17,18} the potential effects of the newer volatile anaesthetics such as isoflurane remain unclear, and the topic still initiates recent discussion.^{3,5} However, the potential health risk of chronic occupational exposure to gaseous anaesthetics has led to the initiation of control limits to reduce anaesthetic gas exposure (table 1). NIOSH, for example, has specified that in general one is not able to identify a safe level of exposure to waste anaesthetic gases.¹⁹ It therefore recommends that the risk be minimised by “reducing exposures to the greatest extent possible”. The NIOSH recommendation for all volatile anaesthetic exposure is a ceiling of 2 ppm over the total exposure time.¹⁹ Interestingly, the recommended exposure levels for volatile anaesthetics in Europe are considerably greater: 5–50 ppm as a time weighted average over an 8 hour working day.²

Compared with previous studies under similar working conditions,^{2,20} measured values were in general higher, but did not violate the European control limits for nitrous oxide and isoflurane. The NIOSH recommendations are strict, and our values were low for nitrous oxide but violated the NIOSH ceiling value of 2 ppm for isoflurane. The reasons are a higher percentage of uncuffed anaesthesia and open system anaesthesia especially for small animals. Due to the measured values and the type of anaesthesia, this working environment seems to be comparable with that for paediatric anaesthesia.²¹

Micronuclei consist of DNA material, which is lost from the cell nucleus during mitosis. They are generated by chromosomal breakage or by dysfunction of the spindle apparatus. Although the micronucleus assay is widely used to screen chemicals for a genotoxic potential by monitoring chromosomal damage, there is only one report about the formation of micronuclei in people exposed to nitrous oxide.²² Unfortunately, the study lacks the data on exposure and a description of the workplace conditions. Furthermore, it seems unlikely that no volatile anaesthetics (such as halothane or isoflurane) were used in the paediatric operating room which was described. Therefore it is not possible to draw a concise comparisons with our results. In the present study, we showed a higher frequency of micronuclei in people exposed to nitrous oxide and isoflurane although these results were not significant.

The sister chromatid exchange test measures the number of exchanges between the two chromatids of a chromosome and is widely used to screen chemicals for possible mutagenicity. By contrast with the micronuclei test, some controversial studies exist on the occupational exposure and induction of sister chromatid exchanges.

Husum and Wolf compared nurse anaesthetists and male anaesthesiologists with non-exposed female nurses and female secretaries.²³

No influence of the anaesthetics halothane and nitrous oxide could be detected. However, the study lacked environmental measurements and sufficient matching of sex, age, and smoking habits. In another study with environmental monitoring the group compared anesthesiologists, surgical operating room nurses, and circulating nurses with non-exposed female controls.²⁴ Although the control group showed the lowest frequency of sister chromatid exchange, the difference was not significant. Also, in that study the population was not matched. Lamberti *et al* showed differences between controls and exposed operating room personnel (to halothane, enflurane, isoflurane, and nitrous oxide), but this was not significant.²⁵ As in the previous studies, matching and environmental monitoring was missing.

By contrast, Natarajan and Santhiya found that the mean frequency of sister chromatid exchange doubled in 20% of the exposed people compared with controls and suggested a possible risk of cytogenetic damage for operating room staff.²⁶ Sardas *et al* found an increased sister chromatid exchange frequency when studying 67 people working in the operating room exposed to unknown amounts of halothane and nitrous oxide and 50 controls.²⁷ Although in both studies data on occupational exposure were not available, they nevertheless indicate a potential genetic risk when exposed to waste anaesthetic gases. Karelova *et al* found a difference between operating room personnel exposed to halothane (9–490 mg/m³) and controls.²⁸ In this study, for the first time, exposed and control groups were comparable for age, smoking habits, and drug intake. Also occupational monitoring of halothane, but unfortunately not nitrous oxide, had been performed.

By contrast with the previous studies, we showed that relatively low doses of inhalational anaesthetic gases caused the formation of sister chromatid exchange in operating room personnel. However, the main limitations of our study are (a) that we are not able to distinguish between the potential genotoxic effects of nitrous oxide and isoflurane, and (b) that we were not able to show a real dose dependency because our study group was too small. Therefore, additional studies are needed to clarify whether higher or lower concentrations of waste anaesthetic gases cause genetic damage. It is especially necessary to determine whether the observed trend to induce micronuclei can be verified.

Nevertheless, we can conclude that even an exposure to low concentrations of waste anaesthetic gases leads to an increased risk of genetic damage. Whether the genetic damage found could result in cancer or other unfavourable health outcomes remains unclear, provided an otherwise healthy subject has sufficient DNA repair mechanisms, and no other health risks—for example, cigarette smoking, immune deficiencies, consuming illness, or other additional potential genetic hazards are present.

Without doubt, these increased micronuclei and sister chromatid exchange rates may be

relevant in the long term and need further investigation.

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