ORIGINAL ARTICLE

Occupational exposure of midwives to nitrous oxide on delivery suites

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Aims: To compare environmental and biological monitoring of midwives for nitrous oxide in a delivery suite environment.

Methods: Environmental samples were taken over a period of four hours using passive diffusion tubes. Urine measurements were taken at the start of the shift and after four hours.

Results: Environmental levels exceeded the legal occupational exposure standards for nitrous oxide (100 ppm over an 8 hour time weighted average) in 35 of 46 midwife shifts monitored. There was a high correlation between personal environmental concentrations and biological uptake of nitrous oxide for those midwives with no body burden of nitrous oxide at the start of a shift, but not for others.

Conclusions: Greater engineering control measures are needed to reduce daily exposure to midwives to below the occupational exposure standard. Further investigation of the toxicokinetics of nitrous oxide is needed.

Nitrous oxide is used as an analgesic during labour. A number of epidemiological studies have linked occupational exposure to nitrous oxide with spontaneous abortions, congenital abnormality, and reduced rates of fertility, including reported effects in midwives.¹⁻⁷ The evidence is equivocal due to problems associated with verification of exposure and validation of reproductive events. Nevertheless this evidence, as well as the known effects of nitrous oxide on folate synthesis, has influenced the setting of occupational exposure standards (OES).

In the UK the (OES) set for nitrous oxide is 100 ppm over an eight hour time weighted average (TWA).⁸ There are also requirements to have 5-6 air changes per hour within delivery rooms⁹ to control levels of waste anaesthetic gas. High levels of nitrous oxide have been reported in delivery rooms,¹⁰⁻¹¹ and a previous survey of levels of nitrous oxide in healthcare facilities had identified midwifery suites as being a particular problem.¹² This made use of direct reading instrumentation, and so was expensive in manpower resource; it was therefore decided to investigate the potential usefulness and acceptability of passive environmental sampling to measure exposures in midwifery.

In order to obtain a better estimate of personal health risk, the measurement of uptake has been proposed. The most widely accepted method of biological sampling is measurement of urinary excretion, and a number of studies have looked at levels of urinary nitrous oxide using gas chromatography.¹³⁻¹⁸ A biological exposure index (BEI) of 55 µg/l for nitrous oxide has been recommended in urine, as this is the biological value which was obtained after four hours of an average environmental exposure to 100 ppm.¹⁹ It was therefore also decided to explore the relation between exposure and uptake.

METHODS

In hospital 1, 15 midwife shifts were monitored, two of which were the same individual. In hospital 2, 35 midwife shifts were monitored; 20 individuals were monitored on one occasion only, four individuals were monitored on two occasions, one on three occasions, and one on four occasions.

In order to deliver samples to the laboratory on the day of sampling, the sampling period was chosen to be four hours (that is, half a shift) rather than eight hours. Therefore each midwife wore a passive sampling tube for the first four hours of their shift, which was placed on the lapel within the breathing zone. The steel tube was packed with molecular sieve 5A supplied by Markes International, with a diffusive cap on the top. Urine samples were collected at the start of the shift to obtain a baseline measurement; at the end of the four hour monitoring period each midwife provided a second sample. Midwives completed a simple questionnaire, which asked for information on smoking, and alcohol consumption in the past 24 hours, and what medication, if any that the midwife was taking. The questionnaire also asked which delivery rooms the midwife had attended during the monitoring, how many births were involved, and whether nitrous oxide was used. Where nitrous oxide had been used, the midwife was asked to estimate the length of time of use and how long they had been present in the room during use.

At the end of the monitoring period the passive sampling tube was sealed and sent for analysis by thermal desorption and gas chromatography. Environmental sampling tubes were thermally desorbed at 165°C in forward flush direction for three minutes with a flow rate of 30 ml/min helium using a Perkin-Elmer ATD-400. Analysis was performed using a Perkin-Elmer Autosystem XL gas chromatograph. A 60 m × 0.32 mm Gas Pro column was used with inlet pressure of 22 psi helium. The oven programme was: 10 minutes isothermal at 150°C, 250°C for 2 minutes post-run; nitrous oxide elutes at 7.2 minutes. Detection was by electron capture at 340°C. For calibration, a static 2% gas mixture in air was prepared by syringe addition of 20 ml nitrous oxide to an IL calibrated glass flask. Clean molecular sieve 5A tubes were fitted to a spare ¼ inch GC port and purged with helium. Aliquots of 0.01-10 ml of the diluted nitrous oxide mixture were injected into the calibration tubes.

Abbreviations: TWA, time weighted average; OES, occupational exposure standard

Main messages

- Personal environmental levels of nitrous oxide exceeded the occupational exposure standard for 70% of midwife shifts monitored.
- There was a high correlation between environmental concentrations and biological uptake of nitrous oxide for midwives with no body burden of nitrous oxide at the start of their shift.
- Approximately 50% of midwives had non-zero baseline values of nitrous oxide in their urine on arrival at the workplace and 50% of these midwives had very high levels.
- The environmental or occupational determinants of these non-zero baseline values warrants further research.
- Environmental control measures will be required to reduce the high environmental levels observed in practice.

Urine was collected in a sample bottle with a screw cap. Sterile receptacles were provided for convenience of urine collection, with subsequent decanting into the sample bottle. Once the sample had been collected, it was taken to the laboratory, where it was either analysed straight away or put into the freezer. Where samples were taken from the afternoon shift, the second samples were put into a freezer for storage overnight. Determination of nitrous oxide concentration in urine was by headspace analysis and gas chromatography, and followed the procedure published by Sonander and colleagues.¹⁴ A 10 ml urine sample was taken from the sample bottle directly into a 20 ml gas tight vial equipped with a silicone septum. The gas tight vial was incubated in a water bath at 37°C for 20 minutes, and then a 50 µl sample of the headspace gas above the urine was taken using a gas tight syringe and injected directly into the gas chromatograph. All such gas chromatograph injections were performed in triplicate. The gas chromatograph was a Hewlett Packard 5890, Series 2, fitted with Electron Capture Detection. An HP Plot Q, 30 m × 0.53 mm ID column was used; the carrier gas was 5% methane in argon with molecular sieve and oxygen trap. Conditions were: column flow rate 6 ml/min, split vent 30 ml/min, septum purge 3 ml/min, auxiliary gas 50 ml/min, anode purge 3 ml/min, oven temperature 30°C, injector temperature 80°C, and detector temperature 250°C. The retention time for nitrous oxide was 3.8 minutes. External calibration was performed by injecting 50 µl nitrous oxide calibration gas (24 ppm in air) supplied by Alltech. The reproducibility associated with sampling and analysis was determined by taking three samples from a number of individuals on several occasions for each type of sampling.

Ventilation checks were carried out in each of the delivery rooms in both the hospitals monitored, by monitoring the decay of a marker gas using an infrared spectrophotometer.²⁰

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 10.

RESULTS

In the sample of 46 midwives over the four hour measurement period, five midwives had TWA exposures in excess of 10 times the OEL, five in excess of 5 times the OEL, 13 in excess of 2 times the OEL, and of the 46 midwives, only 13 had TWA exposures below the OEL. The interindividual

Policy implications

- High exposures of midwives to nitrous oxide on delivery suites is likely to be widespread in the UK.
- The clearance of nitrous oxide from tissues may take longer than was believed to be the case, which may have implications for the occupational exposure standard for nitrous oxide.
- It may be that exposure to nitrous oxide outside of the workplace is widespread and significant.

environmental concentrations were in the range 2.4–1300 ppm, with a mean level of 313 ppm and standard deviation of 358. The coefficient of variation of measurement of repeated samples from an individual was 3–4.8% over the concentration range 10–150 ppm. For urine sampling the coefficient of variation was 6.7%.

In only three midwives was there no nitrous oxide present in the urine after a four hour period. Twenty two midwives had non-zero values of nitrous oxide in their baseline urine samples (that is, immediately before starting their shift); 12 of these had concentrations of nitrous oxide in excess of 27 µg/l, which is the biological exposure limit in Italy. In five of these, four from hospital 1 and one from hospital 2, the baseline urine concentrations were higher than those found in the second sample after four hours occupational exposure. We were not able to identify any significant differences between the working environment or work practices between the two hospitals, which could explain why a greater number of midwives in hospital 1 came into this category. The non-zero baseline urinary concentrations were in the range 3–174 µg/l, with a mean concentration of 44 µg/l and standard deviation of 51 µg/l.

The unexpected observation of non-zero values of nitrous oxide in the baseline urine values of approximately half of the midwives sampled, and of high values for 12 of these raises questions concerning the value of a routine occupational monitoring programme for urinary measurement of nitrous oxide. It also complicates interpretation of the inter-relationships between final urinary concentration and personal environmental concentration.

To explore occupational exposure in the total sample, for each individual the baseline value of urinary concentration was subtracted from the final value of urinary concentration. This will skew the data in a manner dependent on the kinetics of tissue clearance of nitrous oxide present in their urine at the start of a shift; a further complication was that for five midwives the baseline urine concentrations were higher than the final concentrations.

Figure 1 presents environmental levels and urinary levels of nitrous oxide for 46 midwives. The relation is described by the regression equation:

$$\text{Urinary concentration} = 0.275 \times \text{environmental concentration} \quad (p < 0.001)$$

The urinary concentrations in the second urine samples were in the range 0–1102 µg/l (mean 114 µg/l, standard deviation 191 µg/l). Twenty eight midwives had urinary concentrations in excess of 27 µg/l in their second sample.

The ventilation checks carried out showed that in hospital 1, eight of nine, and in hospital 2, six of 11 did not meet the requirements of 5–6 air changes per hour.⁹ Neither delivery suite had working access to scavenging systems for nitrous oxide.

Figure 1 Relation between environmental and urinary levels of nitrous oxide.

Out of the 46 midwife shifts monitored, on six occasions the midwife attended two delivery rooms, and therefore correlation between exposure and the ventilation of the delivery rooms was not possible. For the remaining 40 midwife shifts monitored, the midwife remained in one delivery room for the duration of the monitoring period. In hospital 1, the midwife only attended one delivery room on 11 monitoring occasions. All the rooms monitored had ventilation rates below those recommended. In hospital 2, the midwife only attended one delivery room on 29 monitoring occasions. Of the delivery rooms monitored, four had ventilation rates below those recommended.

DISCUSSION

Nitrous oxide is considered to be of low solubility in blood or in other biological tissues. During absence overnight from the work environment, occupational dose should be completely cleared out of the body storage reservoirs.

We found that approximately half of our samples of 46 midwives had non-zero baseline values of nitrous oxide in urine, of which 12 had very high levels.

The kinetics of absorption of nitrous oxide and then tissue clearance are not known quantitatively. It is known that nitrous oxide is eliminated in the kidney by a diffusion process determined by the equilibration of partial pressures in urine and plasma. As a result, the concentration of nitrous oxide in urine is independent from urine output, and urine leaving the kidneys equilibrates with gas in arterial blood with the bladder serving as a collecting and mixing vessel. Thus urinary concentration can be considered as an integrator over time, which indicates uptake over the duration of exposure.

Pre-shift urine samples were collected as soon as the midwife appeared on the delivery suite. Since urinary concentration is an integrator over time, any brief adventitious exposure of a midwife to nitrous oxide between entry to the hospital and reporting to the delivery suite is highly unlikely to have altered the concentration in the urine in the bladder.

It has been suggested in the literature that certain Gram negative bacilli which may be present in the urinary tract during urinary tract infections (UTI) can produce nitrous oxide. However, the prevalence of high levels of nitrous oxide in our sample of midwives is much higher than the prevalence of UTI in women; furthermore, not all UTI is caused by Gram negative bacilli. It is therefore unlikely that UTI is the source of high baseline levels in urine prior to the commencement of the shift.

Other possibilities are non-occupational exposure to nitrous oxide, for example, from gas fires in the home, motor vehicle exhaust gases, or from spray cans for foodstuffs or deodorants. Given the ubiquity of these sources of exposure, if they were contributing to the high baseline levels of nitrous oxide in urine observed in 22 women, we would not expect 24 women to have an absence of nitrous oxide in their baseline urine. The most likely explanation of nitrous oxide in baseline urine is perhaps that tissue clearance occurs over much longer time periods than has been previously thought. Thus the 22 non-zero baseline values may relate to previous but recent occupational exposure. The 24 zero baseline values would then relate to women who have not been as recently occupationally exposed, and there may be an unrecognised accumulating effect of exposure.

The presence of nitrous oxide in baseline urine complicates an evaluation of the relations between environmental exposure and uptake as measured by urinary concentrations. In order to explore this, the group of 24 midwives with no nitrous oxide in their baseline urine have been analysed separately, as well as examining the group as a whole.

For the 24 midwives there was a high correlation between personal environmental exposure and urinary concentrations. This shows that a TWA personal environmental sample is a good measure of integrated biological uptake for women with no nitrous oxide in their urine at baseline.

The occupational exposure limits in the UK relate to environmental levels, but ideally these should relate to the measure that actually reflects uptake—that is, urinary concentration. These data show that there is a need to explore the kinetics of nitrous oxide absorption over the sort of time scales of relevance in occupational health practice. This will require tracking a number of individuals over a period of days, spanning both occupational exposure days and non-occupational exposure days. Urine could be sampled periodically, and the role of accumulated uptake and washout explored on the basis of shift pattern and exposure.

CONCLUSION

Monitoring for nitrous oxide exposure by personal environmental sampling using passive diffusion tubes, or by collection of urine samples, was found to be acceptable to midwives and was convenient. The use of analytical gas chromatography for determination of nitrous oxide in urine samples and environmental samples is accurate and sufficient for this purpose. The reproducibility of each type of sampling was also satisfactory. Our data show that midwives are routinely exposed to levels of nitrous oxide in excess of the occupational exposure limit (OEL). Environmental control measures and/or changes in work practices will be necessary to reduce the high environmental levels observed; environmental monitoring may be undertaken to check the efficacy of such measures in reducing environmental levels.

There is a high correlation between environmental exposure measurements and measures of biological uptake (that is, urinary concentrations) for midwives with no nitrous oxide in their urine at the commencement of their shift. However, we observed approximately half of the midwives studied to have significant levels of nitrous oxide in their urine at baseline. Thus it would appear that nitrous oxide is not cleared from the body as quickly as previously thought. Consequently, depending on exposure patterns and shift patterns, an individual may accumulate body burden of nitrous oxide. This may occur for an individual, even if environmental measurement falls below the OEL. We suggest that urine samples pre- and post-shift will allow a reliable estimate of nitrous oxide exposure for persons who have none detectable in the pre-shift sample. In the case of nitrous

oxide being present in the pre-shift sample, the possible reasons, including bioaccumulation with the potential for increased susceptibility to adverse effects, should be considered.

Quantification of the clearance of nitrous oxide from the body would permit personal occupational uptake to be measured by biological monitoring.

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REFERENCES

- Rowland AS, Baird DD, Weinberg CR, *et al.* Reduced fertility in women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992;**327**:993-7.
- Baird PA. Occupational exposure to nitrous oxide—not a laughing matter. *N Engl J Med* 1992;**327**:1026-7.
- Kugel G, Letelier C, Attallah H, *et al.* Chronic low level nitrous oxide exposure and infertility. *J Dent Res* 1989;**68**:313.
- Hemminki K, Kyyronen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytotoxic drugs and other potential hazards in hospital based on registered information of outcome. *J Epidemiol Community Health* 1985;**39**:141.
- Monson RR. *Occupation and reproduction. Occupational epidemiology.* BOCA Raton: CRC Press, 1990:188.
- Alhborg JR, Axelsson G, Bodin L. Nitrous oxide exposure and subfertility among Swedish midwives. *Int J Epidemiol* 1996;**25**:783-90.
- Schumann D. Nitrous oxide anaesthesia: risks to health personnel. *Int Nurs Rev* 1990;**37**:214-17.
- HMSO. *Control of Substances Hazardous to Health (COSHH) Regulations: Approved Codes of Practice.* London: HMSO, 1999.
- Health Services Advisory Committee (HSAC). *Anaesthetic agents: controlling exposure under COSHH.* HSAC, 1996.
- Munley AJ, Railton R, Gray WM, *et al.* Exposure of midwives to nitrous oxide in four hospitals. *BMJ* 1986;**293**:1063-4.
- Newton C, Fitz-Henry J, Bogod D. The occupational exposure of midwives to nitrous oxide—a comparison between two labour suites. *Int J Obstet Anaesth* 1999;**8**:7-10.
- Henderson KA, Matthews IP. An environmental survey of compliance with occupational exposure standards (OES) for anaesthetic gases. *Anaesthesia* 1999;**54**:941-7.
- Trevisan A, Gori GP. Biological monitoring of nitrous oxide exposure in surgical areas. *Am J Ind Med* 1990;**17**:357-62.
- Sonander H, Stenquist O, Nilsson K. Urinary nitrous oxide as a measure of biologic exposure to nitrous oxide anaesthetic contamination. *Ann Occup Hygiene* 1983;**27**:73-9.
- Imberti R, Preseglio I, Imbriani M, *et al.* Low flow anaesthesia reduces occupational exposure to inhalation anaesthetics. *Acta Anaesthesiol Scand* 1995;**39**:586-91.
- Imbriani M, Ghittori S, Pezzagno G. The biological monitoring of inhalation anaesthetics. *Gionale Italiano Di Medicina Del Lavoro Ed Ergonomia* 1998;**20**:44-9.
- Gobba F, Ghittori S, Imbriani M, *et al.* The urinary excretion of solvents and gases for the biological monitoring of occupational exposure: a review. *The Science of the Total Environment* 1997;**199**:3-12.
- Accorsi A, Barbieri A, Raffi G, *et al.* Biomonitoring of exposure to nitrous oxide, sevoflurane, isoflurane and halothane by automated GC/MS headspace urinalysis. *Int Arch Occup Environ Health* 2001;**74**:541-8.
- Imbriani M, Ghittori S, Pezzagno G, *et al.* Nitrous oxide in urine as biological index of exposure in operating room personnel. *Applied Industrial Hygiene* 1988;**3**:223-7.
- MDHS 73. *Measurement of air change rate in factories and offices.* Croner, 1992.