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Short Communication

Accumulation and loss of halothane and enflurane in blood from rats exposed to pollutant concentrations

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Introduction

Data on operating theatre air pollution by traces of anaesthetic gases have been collected by several authors [1–3]. Further epidemiological studies on the hazards for personnel working in anaesthetizing and postanaesthetic recovery locations [4–7] suggested a possible causal relationship between reported occupational disease and the waste anaesthetic gases. Detectable levels of halothane in the venous blood of anaesthetists and other surgical staff have been reported [8–12]. Wolff [13] found traces of this anaesthetic in the adipose tissue of rats as long as 5 days after subchronic exposure to pollutant concentrations (3 h daily for 5 days). Although operating theatre personnel may be subject to increasing body levels of anaesthetic agents, there seem to be no published data on the accumulation or the removal of inhalation anaesthetics after lengthy occupational exposure to trace concentrations. This study provides pharmacokinetic data on the levels of two commonly used inhalation anaesthetics, halothane and enflurane, during and after chronic exposure to trace concentrations.

Experimental

Male Wistar rats (200 ± 10g) were housed under constant environmental conditions and allowed access to food and water *ad libitum*. After an adaptation period the animals

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were placed in sealed plastic chambers and exposed to air contaminated with halothane (150 ppm) or enflurane (200 ppm) for 8 h daily. The exposures continued on 5 weekdays for 7 weeks, with a break from 4.00 p.m. each Friday to 8.00 a.m. each Monday. Quantitative analyses of halothane or enflurane in rat blood samples were performed at 4.00 p.m. each Friday and 8.00 a.m. each Monday. At the end of the 7-week exposure, blood samples were taken and analysed twice daily (8.00 a.m. and 4.00 p.m.) until the anaesthetics were not detectable. The trace concentrations of halothane and enflurane in the air of the experimental chambers were also measured weekly (each Monday at 12.00 noon).

Analytical method

The anaesthetic concentrations in blood samples from exposed animals and in air samples were detected by gas-chromatography with the head-space technique. Isobutanol was employed as the internal standard.

Materials

Halothane and enflurane as trading products were purchased from Vister and Abbott respectively. All inorganic and organic chemicals were analytical reagents (E. Merck).

Calibration curves

For contaminated air analyses enflurane aqueous solutions were added to sealed 200 glass tubes to produce 100, 200, 300 and 500 ppm nominal concentrations; 10 ml of aqueous isobutanol solution (0.3 mg/ml) were added as an internal standard. For blood determinations 3 ml aliquots of blood containing 0.05, 0.1, 0.5, 1.0 and 2.0 μg/ml were added to sealed 200 ml glass tubes. The tubes and vials were placed in a thermostatic oven (50°C) for 2 h, and 1–2 ml of the head-space air was injected into a Carlo Erba 4200 gas-chromatograph equipped with a glass column (2 m × 3 mm I.D.) packed with 25% PEG 400 on Anakrom C22A 40–50 mesh and a flame ionization detector. Oven, detector and injector temperatures were 100°, 150° and 160°C respectively. The nitrogen flow rate was 30 ml/min.

Air and blood analyses

Concentrations of halothane and enflurane in the air of the experimental chambers were determined by the procedure described above, the values at different times being calculated with the appropriate calibration curves. Each determination was performed in triplicate. The blood analyses were performed as described above on 3 ml samples of blood from five animals exposed to each anaesthetic agent. Blood from control animals was also analysed.

Results

The concentrations of halothane and enflurane in the air of the experimental chambers during the treatment period are shown in Table 1. Blood levels of the anaesthetic agents are shown in Table 2. Figure 1 illustrates the increased blood levels of the anaesthetics measured at 4.00 p.m. every Friday and, after the week-end break, at 8.00 a.m. every Monday. The decreasing anaesthetic levels in blood samples taken after the exposure period are shown in Table 3 and Fig. 2.

Table 1
Concentrations of halothane and enflurane in the air of experimental chambers

	Halothane (ppm ± S.D., $n = 3$)	Enflurane (ppm ± S.D., $n = 3$)
1st Monday	140 (1.5)	188 (1.0)
2nd Monday	130 (2.0)	190 (2.0)
3rd Monday	135 (1.0)	168 (2.1)
4th Monday	142 (0.9)	175 (1.3)
5th Monday	138 (1.2)	195 (1.8)
6th Monday	130 (1.5)	190 (1.6)
7th Monday	132 (0.8)	185 (1.5)
Average ± S.D., $n = 7$	135 (4.8)	184 (9.5)

Table 2
Halothane and enflurane concentrations in the blood of exposed rats

Day		Halothane (μg/ml ± S.D., $n = 5$)	Enflurane (μg/ml ± S.D., $n = 5$)
1st week	Monday	0.00	0.00
	Friday	0.20 (0.02)	0.10 (N.D.)
2nd week	Monday	0.04 (N.D.)	N.D.
	Friday	0.32 (0.02)	0.42 (0.03)
3rd week	Monday	0.05 (N.D.)	N.D.
	Friday	0.43 (0.03)	0.60 (0.04)
4th week	Monday	0.07 (N.D.)	0.04 (N.D.)
	Friday	0.47 (0.03)	0.75 (0.04)
5th week	Monday	0.14 (0.02)	0.06 (N.D.)
	Friday	0.55 (0.03)	1.15 (0.04)
6th week	Monday	0.16 (0.02)	0.09 (N.D.)
	Friday	0.70 (0.04)	1.27 (0.04)
7th week	Monday	0.25 (0.02)	0.11 (N.D.)
	Friday	0.73 (0.04)	1.45 (0.04)

N.D. = not determined.

Table 3
Blood concentrations of halothane and enflurane after the end of the exposure period

Time		Halothane (μg/ml ± S.D., $n = 5$)	Enflurane (μg/ml ± S.D., $n = 5$)
1st day:	8.00 a.m.	0.200 (0.010)	0.150 (0.010)
	4.00 p.m.	0.180 (0.015)	0.120 (0.010)
2nd day:	8.00 a.m.	0.140 (0.013)	0.085 (0.070)
	4.00 p.m.	0.100 (0.090)	0.080 (0.070)
3rd day:	8.00 a.m.	0.080 (0.060)	0.040 (N.D.)
	4.00 p.m.	0.070 (0.050)	0.036 (N.D.)
4th day:	8.00 a.m.	0.045 (N.D.)	0.010 (N.D.)
	4.00 p.m.	0.030 (N.D.)	N.D.
5th day:	8.00 a.m.	N.D.	N.D.

N.D. = not determined.

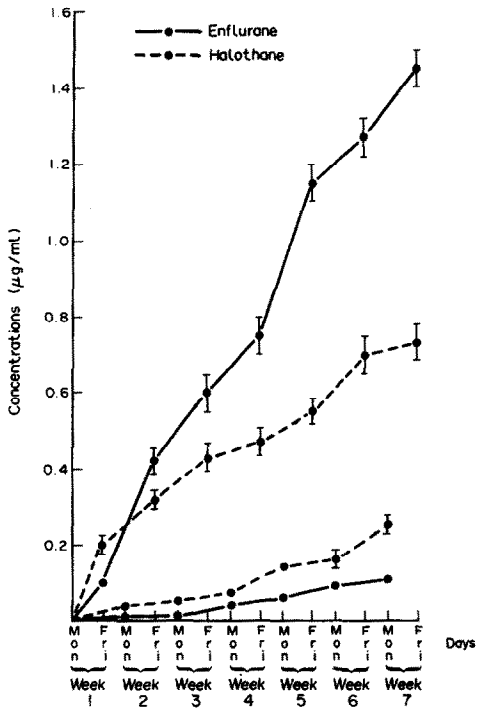

Figure 1
Blood levels (µg/ml) of halothane and enflurane during 7 weeks exposure to pollutant concentrations.

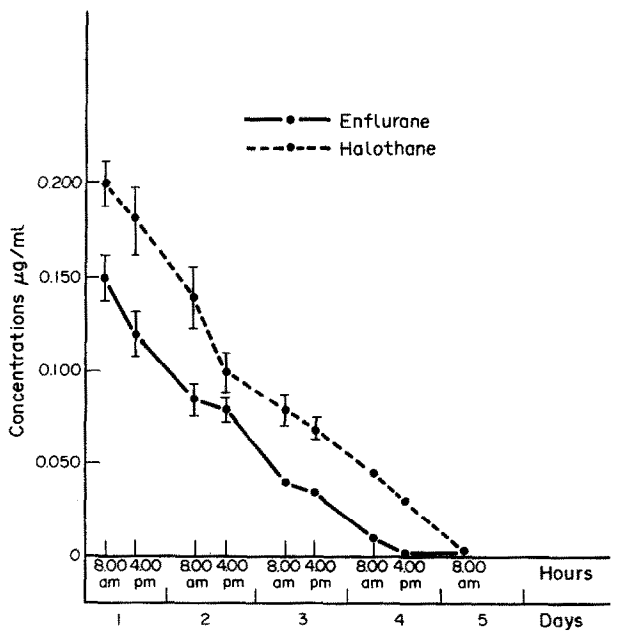

Figure 2
Blood levels (µg/ml) of halothane and enflurane after the last exposure to pollutant concentrations.

Discussion

The results show that halothane and enflurane accumulate in animals housed in an environment simulating that of an operating theatre. This observation is in agreement with previous pharmacokinetic studies [14, 15] and with the clinical observations of Corbett [16] and Corbett and Ball [17] who found halothane traces in the exhaled breath of anaesthetists as long as 74 h after routine occupational exposures. The differences in retention and excretion of the two anaesthetic agents may be explained by their different oil/gas partition coefficients (98 for enflurane, 220 for halothane). All the results on halothane absorption, storage and removal show a pharmacokinetic profile very much slower than that of enflurane. This also explains the greater increase of residual blood halothane at 8.00 a.m. every Monday, after the week-end breaks. This period without exposure appears to be insufficient for the complete removal of residual anaesthetic gases. This is confirmed by the finding that detectable blood concentrations are still present 4 days after the last exposure.

Extrapolating these findings to clinical conditions, it may be assumed that personnel exposed to halothane and/or enflurane during their working day accumulate the drugs in their tissues and release it slowly. Thus the day-to-day accumulation of anaesthetics can take place. Although no direct causal relationship has been established between the health problems of operating personnel and chronic exposure to low concentrations of anaesthetic gases, consideration of the potential health hazards suggests that efficient removal of waste anaesthetic gases from the working environment is desirable.

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