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Occupational Exposure to Halothane Results in Enzyme Induction in Anesthetists

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To determine whether exposure to trace concentrations of halothane resulted in enzyme induction, antipyrine pharmacokinetics were measured in six anesthetists before and after ten days of exposure to waste halothane. Antipyrine clearance increased by 29 per cent, a clinically small but statistically significant ($P < 0.025$) change, whereas the apparent volume of antipyrine distribution remained unchanged, indicating that halothane induces antipyrine metabolism. The implications of this finding for anesthetists cannot be simply defined. Enzyme induction may be beneficial or harmful, depending on the relative toxicities of the unbiotransformed parent compounds and their metabolites. (Key words: Anesthetics, volatile: halothane; trace concentrations. Biotransformation (drug): enzyme induction. Metabolism: enzyme induction. Operating rooms: contamination.)

EXPOSURE OF RATS to approximately 0.5 MAC concentrations of the volatile anesthetic agents, chloroform, diethyl ether, enflurane, fluroxene, halothane, isoflurane, and methoxyflurane, leads to a reduction in hexobarbital sleep time, suggesting that administration of these drugs can cause enzyme induction.[1] Additional evidence of enzyme induction after exposure to volatile anesthetic agents is found in animal studies that have demonstrated conversion of rough to smooth hepatic endoplasmic reticulum[2] and increased levels of cytochrome P-450 and other enzymes involved in drug metabolism.[1,3–5] From these animal studies it has come to be accepted that chronic exposure to subanesthetic concentrations of the volatile inhalational agents results in induction of hepatic drug-metabolizing enzymes.

Studies of the enzyme-inducing effects of anesthetic agents in anesthetized human subjects are rare. Studies in anesthetists at occupational levels of anesthetic exposure found in unscavenged operating rooms also are infrequent. Reported results of such studies are difficult to interpret because of inadequate controls, exposures to more than one anesthetic agent, and the lack of a specific noninvasive *in vivo* test for enzyme induction.[6–8] The latter problem is not unique to studies of anesthetic drugs: however, an indirect measurement of enzyme induction, the antipyrine test, has been devised to examine rates of drug metabolism.[9] The test involves comparison of antipyrine pharmacokinetics in the same subjects: initially in an environmentally stable, controlled state, then after imposition of a single environmental change. Under these circumstances increased antipyrine metabolic clearance rate (Cl) is accepted as reflecting an increase in hepatic mixed-function oxidase activity. In the present study, enzyme induction in anesthetists was studied by measuring salivary antipyrine pharmacokinetics before and after chronic inhalation of measured, trace concentrations of halothane.

Materials and Methods

The subjects were six anesthetists who had not been exposed to halothane for the preceding two months. None of the anesthetists used drugs or was a heavy user of alcohol. Three smoked ten or more cigarettes a day; the others did not smoke. Exposure to waste halothane occurred in a pediatric hospital where anesthetists administered halothane–oxygen anesthesia for ear, nose and throat operations. Exposures took place during two five-day periods, separated by a two-day interval. Halothane concentrations of as much as 4 per cent were administered for induction of anesthesia with oxygen flows of 4–8 l/min; halothane concentrations of 0.5–2.5 per cent were employed for maintenance. Nitrous oxide was not used. A nonrebreathing system without waste-gas scavenging was employed.

To quantitate exposure to halothane, a daily time-weighted average air sample was obtained from the anesthetist's breathing zone by use of a portable sampling pump and collection bag. Detailed methods and results of this part of the study have been reported.[10]

Antipyrine pharmacokinetics were measured two days before and within 24 hours after termination of

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TABLE 1. Data for Individual Anesthetists*

	Antipyrine Half-life ($t_{1/2}$) (hr)		Volume of Antipyrine Distribution (l/kg)		Antipyrine Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)		Smoke
	I	II	I	II	I	II	
Anesthetist 1	13.40	10.00	0.67	0.67	0.68	0.83	–
Anesthetist 2	11.25	6.05	0.54	0.57	0.55	1.01	–
Anesthetist 3	8.50	6.55	0.57	0.55	0.72	0.77	–
Anesthetist 4	8.15	5.60	0.63	0.56	0.91	1.18	+
Anesthetist 5	14.75	10.50	0.71	0.70	0.52	0.79	+
Anesthetist 6	8.75	8.75	0.51	0.53	0.67	0.70	+
MEAN ± SE	10.80 ± 1.14	7.91 ± 0.86	0.61 ± 0.03	0.60 ± 0.03	0.68 ± 0.06	0.88 ± 0.07	
	t = 3.86 $P < 0.01$		t = 0.56 $P > 0.2$		t = 3.10 $P < 0.025$		

* I = studies prior to exposure to halothane; II = studies after exposure to halothane.

the last exposure to halothane. A 3–5-ml control sample of saliva was obtained by voluntary expectoration, following which subjects orally ingested a single 15-mg/kg dose of antipyrine. Five or six salivary samples then were obtained at approximately two-hour intervals for antipyrine analysis, in addition to at least one other sample obtained 18–24 hours after antipyrine ingestion. Salivary antipyrine levels correlate well with plasma levels,[11,12] and the salivary method of sampling is more acceptable to subjects than is repeated venipuncture. Samples were centrifuged to remove particulate matter and the supernatant was frozen for subsequent analysis by the gas–liquid chromatographic method of Prescott *et al.*[13] as modified by Miguet *et al.*[14] Antipyrine pharmacokinetics were calculated assuming a one-compartment open model. Antipyrine half-life ($t_{1/2}$) was calculated by least-squares regression analysis of the exponential decline of antipyrine concentration with time. The apparent volume of antipyrine distribution (V_d) was calculated as $V_d = D/C_0$, where D is the dose of antipyrine ingested and C_0 the salivary concentration extrapolated to time zero. Metabolic clearance of antipyrine was calculated from the formula, $Cl = (0.693 \cdot V_d)/t_{1/2}$.

The mean and the standard error of the mean (SE) were calculated for antipyrine $t_{1/2}$, Cl, and V_d. Paired t tests were used for statistical comparisons; $P < 0.05$ was considered significant.

Results

Exposure to trace concentrations of halothane resulted in a statistically significant ($P < 0.025$) but clinically small 29 per cent increase in antipyrine Cl and no change in V_d; this led to a 27 per cent decrease ($P < 0.01$) in $t_{1/2}$ (table 1). Representative data from one of the subjects are presented in figure 1. Results were not significantly influenced by whether the anesthetists smoked cigarettes (however, the number of individuals studied was small). Average daily halothane concentration in the operating room was 19.2 ± 3.2 ppm; average daily duration of exposure was 3.8 ± 0.2 hours.[10]

Discussion

A number of compounds, including antipyrine, aminopyrine, phenylbutazone, and diazepam, have been used to measure the effect of a single environmental perturbation on the drug-metabolizing capacity of the liver.[15,16] Of the test compounds, antipyrine is probably the best because it is: essentially nontoxic; rapidly and completely absorbed from the gastrointestinal tract and distributed in total body water; minimally bound to plasma and tissue proteins; metabolized almost exclusively by the hepatic mixed-function oxidase system; not eliminated by the kidneys.[17,18] Introduction of a gas–liquid chromatographic method for measurement of antipyrine in biologic fluids,[13] development of an antipyrine radioimmunoassay technique,[19] and, most recently, the use of saliva as a noninvasive source of antipyrine-containing body fluids,[11,12] have broadened the applications of the antipyrine test. Individuals treated with numerous drugs, exposed to various environmental conditions and chemicals, and afflicted with many diseases have been investigated by use of antipyrine as an indicator of hepatic drug-metabolizing capacity. A recent review by Vessel,[9] one of the originators of the antipyrine test for drug disposition studies, lists more than 50 publications describing such studies.

Several basic advances in knowledge of drug biotransformation have evolved from these studies. One is that there may be large (two- to fourfold) interindividual differences in the capacity to metabolize a given drug among normal subjects exposed to apparently homogeneous environmental conditions.

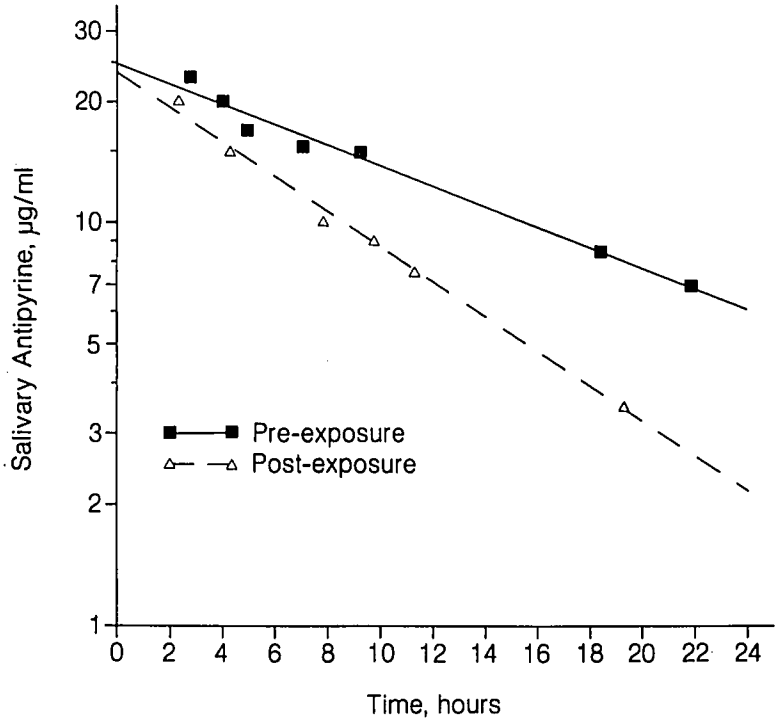

FIG. 1. Salivary antipyrine levels in a single subject before and after exposure to trace concentrations of halothane. Antipyrine clearance increased from 0.55 to 1.01 $ml \cdot min^{-1} \cdot kg^{-1}$, while the volume of distribution remained essentially unchanged, suggesting that induction of antipyrine metabolism had occurred.

This emphasizes a limitation of studies of antipyrine pharmacokinetics, *i.e.*, extrapolation of results from one subject to another or from one drug to another may not be justified. On the other hand, biotransformation of a given drug by an individual is highly reproducible when environmental conditions remain stable, even when studies are carried out over a period of several months. Thus, the effect of a single event, whether a drug treatment, environmental alteration, or disease, on an individual's ability to metabolize a test drug may be assessed by testing the subject before and after the event has occurred. From these data, it is then possible to make a statement about the individual's hepatic mixed-function oxidase activity, at least so far as metabolism of the test drug is concerned, and perhaps for drugs with similar structures, properties, and rate-limiting steps of metabolism.

This information should allow us to appreciate some of the limitations of the present study and those of other studies that have examined the effects of occupational exposure to anesthetics on drug biotransformation. In the present study, antipyrine pharmacokinetic measurements were made in all anesthetists prior to and after exposure to halothane, avoiding the problem of interindividual differences in metabolism. Also, the only apparent change that occurred in the anesthetists' environment was exposure to the single anesthetic agent, halothane, and exposure to this drug was quantitated. Therefore, a firm conclusion can be drawn from this investigation: exposure to occupational concentrations of halothane alters antipyrine disposition in a direction consistent with slight enzyme induction. Other test compounds were not studied, so the effects of exposure to halothane on their biotransformation are a matter of conjecture.

The present study overcomes some of the methodologic problems which occurred in previous investigations.[6–8] Cascorbi[6] administered ^{14}C-halothane to anesthetists working in unscavenged operating rooms and to pharmacists to determine whether occupational exposure to trace concentrations of anesthetic agents resulted in differences in halothane biotransformation. No difference was found. However, that study did not control for interindividual variations in drug biotransformation, nor were the type and amount of exposure to waste anesthetic gases measured. Wood *et al.*[7] examined antipyrine pharmacokinetics in a group of 23 anesthetists and operating room technicians and compared results with data obtained from a previously studied control group of 23 non-anesthetic-exposed subjects of unspecified occupation. Antipyrine Cl in the former group was significantly higher, but $t_{1/2}$ was not different. Again, in their study, interindividual variation in antipyrine metabolism was not controlled for, nor was exposure to waste gases measured. In another study, Harman *et al.*[8] could not demonstrate significant differences in antipyrine Cl and $t_{1/2}$ between a group of 21 anesthetists and a control group of 14 non-exposed subjects. Finally, in a preliminary phase of the present study, we found a

significant difference between values for antipyrine Cl obtained from 15 anesthetists who regularly administered halothane and 16 anesthetists who did not use this agent; the difference in $t_{1/2}$was not significant. The discrepancies among and within these studies probably reflect the large differences in interindividual rates of antipyrine metabolism and differences in exposures to halothane and to other anesthetic agents. Also, there may have been unapparent changes in the subjects' milieus that could have altered V_d, accounting for the discrepancies between Cl and $t_{1/2}$.

In the only other study in which antipyrine pharmacokinetics were measured in the same individuals before and after exposure to anesthetic agents, Harman *et al.*[8] found a 17 per cent increase in the rate of antipyrine Cl and a 22 per cent decrease in $t_{1/2}$. However, in that study, individual exposures to halothane were not measured, and nitrous oxide was also present as a contaminant of operating room air. Although these results are similar to ours, they cannot be attributed with certainty to exposure to trace concentrations of halothane.

The implications of our study for anesthetists working in unscavenged operating rooms cannot be simply defined. Changes in the rate of antipyrine metabolism, 29 per cent, were small compared with the changes of more than 50 per cent that have been found after treatment with enzyme-inducing agents such as phenobarbital.[20] The biotransformation of other compounds was, no doubt, also affected, although this was not measured. However, even if the changes were of greater magnitude, it cannot be said whether they would be associated with adverse or beneficial effects. That would depend on whether the products of biotransformation were more or less harmful than was the unbiotransformed parent compound. Both situations may pertain. For example, if a subject were to receive prolonged methoxyflurane anesthesia, increased biotransformation of this agent to inorganic fluoride would be harmful. On the other hand, if an overdose of a barbiturate were administered, increased biotransformation would shorten the duration of barbiturate effect. At the moment, all that can be said with certainty is that exposure to trace concentrations of halothane induces biotransformation of antipyrine, and possibly of other drugs also.

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