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Title : OCCUPATIONAL EXPOSURE TO HALOTHANE RESULTS IN ENZYME INDUCTION IN ANESTHETISTS

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Introduction. To determine whether exposure to trace concentrations of halothane results in enzyme induction, salivary antipyrine pharmacokinetics were measured in six anesthetists both before and after 10 days of exposure to waste halothane.

Methods. Anesthetists had not been exposed to halothane for the preceding two months; they used no drugs and were not heavy users of alcohol. Exposure took place during two five-day periods, separated by a two-day interval. Halothane concentrations of up to 4 per cent were administered with oxygen flows of 4-8 L/min; nitrous oxide was not used. A non-rebreathing system without waste-gas scavenging was employed. To quantitate exposure to halothane, daily time-weighted average air samples were obtained from the anesthetists' breathing zone.

Salivary antipyrine pharmacokinetics were measured two days before and within 24 hours after termination of the last exposure to halothane. Subjects ingested a single, 15 mg/kg, oral dose of antipyrine following which five or six salivary samples were obtained at approximately two hour intervals for antipyrine analysis, as well as one other sample, 18-24 hours after antipyrine ingestion. Antipyrine pharmacokinetics were calculated assuming a one-compartment open model. Metabolic clearance (Cl) of antipyrine was calculated from the formula, Cl = (0.693 x volume of distribution (Vd)) x half life ($t_{\frac{1}{2}}$). Paired t tests were used for statistical comparisons; $P < 0.05$ was considered significant.

Results. Exposure to trace concentrations of halothane (19.2 ± 3.2 ppm; duration of exposure 3.8 ± 0.2 hrs) resulted in a statistically significant ($P < 0.025$), but clinically small, 29 per cent increase in antipyrine Cl and no change in Vd; this led to a 27 per cent decrease ($P < 0.01$) in $t_{\frac{1}{2}}$ (table).

Discussion. Studies in anesthetists of the enzyme inducing effects of exposure to occupational levels of anesthetic agents are rare. A reason for this is the lack of a specific noninvasive *in vivo* test for enzyme induction. However, an indirect measurement of enzyme induction, the antipyrine test, has been devised to examine rates of drug metabolism. The test involves comparison of antipyrine pharmacokinetics in the same subject; initially, in an environmentally stable, controlled state and then again, after imposition of a single environmental change. Increased antipyrine Cl is accepted under these circumstances as reflecting an increase in hepatic mixed function oxidase activity. In the present study, the only change in the anesthetists' environment was exposure to trace concentrations of halothane. Thus, it can be stated that this exposure resulted in mild enzyme induction. These results are in contrast to those of Cascorbi[1] who could not demonstrate differences in ^{14}C-halothane metabolism (i.e., enzyme induction) between a group of anesthetists exposed to waste anesthetic agents and a non-exposed group of pharmacists.

The implications of this 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 that have been reported after treatment with enzyme inducing agents such as phenobarbital. 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 the unbiotransformed parent compound. Both situations may pertain. For example, if a subject received a long methoxyflurane anesthetic, increased biotransformation of this agent to inorganic fluoride would be harmful. On the other hand, if an overdose of barbiturates were administered, increased biotransformation would shorten the duration of barbiturate effect. What can be said with certainty is that exposure of anesthetists to trace concentrations of halothane in unscavenged operating rooms induces antipyrine biotransformation, and possible that of other drugs.

Reference. 1. Cascorbi HF: Factors causing differences in halothane biotransformation. Int Anesthesiol Clin 12:63-71, 1974.

Table. Antipyrine pharmacokinetic data, Mean ± SE

$t_{\frac{1}{2}}$ (I) hr	$t_{\frac{1}{2}}$ (II) hr	Vd (I) L/kg	Vd (II) L/kg	Cl (I) ml/min/kg	Cl (II) ml/min/kg
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 halothane exposure; (II), Studies after halothane exposure.