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Biotransformation of Halothane and Enflurane in Patients with Hyperthyroidism

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Halogenated anesthetics are commonly administered to patients undergoing thyroid surgery. Their main advantages are that recovery is rapid, which is important in patients susceptible to postoperative airway obstruction, and that they cause only a moderate increase in concentrations of plasma thyroid hormones.[1,2] Although hepatic necrosis has not been reported in patients with hyperthyroidism receiving halogenated anesthetics, administration of halothane, enflurane, and isoflurane has resulted in hepatic necrosis in triiodothyronine (T_3) pretreated rats.[3,4] For this reason, and because patients with Graves' disease often are treated with several drugs that have an effect on the hepatic microsomal enzyme system, we examined the biotransformation of halogenated anesthetics by patients undergoing thyroid surgery. Specifically, we measured halothane and enflurane metabolites after anesthesia in: 1) euthyroid patients having surgical removal of a nonsecreting thyroid tumor; 2) patients with Graves' disease treated preoperatively with propranolol, carbimazole, and phenobarbital; and 3) untreated patients with mild to moderate hyperthyroidism secondary to a toxic adenoma of the thyroid gland.

MATERIALS AND METHODS

Forty patients scheduled for thyroid surgery were assigned to one of three groups according to the type of thyroid disease they had; within each group, patients were randomly assigned to receive either halothane or enflurane. Group 1 consisted of 14 euthyroid patients undergoing surgical removal of a nonsecreting thyroid tumor; five patients received halothane and nine were administered enflurane. Group 2 consisted of 19 patients with Graves' disease undergoing subtotal bilateral thyroidectomy after preoperative preparation with propranolol (30–120 $mg \cdot day^{-1}$), carbimazole (20–60 $mg \cdot day^{-1}$) and phenobarbital (80–500 $mg \cdot day^{-1}$); 11 patients received halothane and eight were given enflurane. All of these patients were considered clinically euthyroid at the time of surgery. Group 3 consisted of seven patients with clinically mild to moderate hyperthyroidism and with laboratory evidence of thyroid dysfunction (mean serum thyroxine [T_4] level [±SD], 14.4 ± 3.4 $\mu g \cdot 100\ ml^{-1}$; serum T_3, 315 ± 85 $ng \cdot 100\ ml^{-1}$; normal values, less than 12.5 $\mu g \cdot 100\ ml^{-1}$ and 200 $ng \cdot 100\ ml^{-1}$, respectively) under-

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TABLE 1. Preoperative Patient Data (Mean ± SD)

	Sex Ratio (M/F)	Age (yr)	Weight (kg)	Heart Rate (beats/min^{-1})	Plasma Creatinine (mg · 100 ml^{-1})	Plasma Protein (g · 100 ml^{-1})
Group 1 (n = 14)	1/13	41 ± 16	56 ± 9	76 ± 21	0.81 ± 0.11	6.8 ± 0.3
Group 2 (n = 19)	7/12	35 ± 9	61 ± 9	79 ± 10	0.81 ± 0.12	6.8 ± 0.4
Group 3 (n = 7)	0/7	48 ± 9	65 ± 7	94 ± 5	0.83 ± 0.10	6.8 ± 0.3

Group 1, euthyroid; Group 2, Graves' disease; Group 3, hyperthyroid.

going surgical removal of a toxic adenoma without any specific preoperative antithyroid medication; four patients received halothane, and three received enflurane. The study was performed in compliance with our institutional review-board policies.

Age, weight, sex ratio, and plasma protein and creatinine concentrations of the three groups of patients are summarized in table 1. All patients were premedicated orally with diazepam, 0.2 mg · kg^{-1}, and atropine, 1 mg; group 2 patients also received 40 mg of propranolol. Anesthesia was induced with thiopental, 5–7 mg · kg^{-1}, and succinylcholine, 1 mg · kg^{-1}, was administered to facilitate tracheal intubation. Anesthesia was maintained with 0.5–1.5% halothane or 1–3% enflurane, with 60% nitrous oxide and 40% oxygen. A single dose of fentanyl, 1.5 μg · kg^{-1}, also was administered. Ventilation was controlled to maintain normal end-expiratory P_{CO_2}. After the end of the surgical procedure, propranolol and sedative therapy were resumed in group 2 patients and continued for 5 days.

Biotransformation of halothane was assessed by determination of serum bromide concentrations measured with x-ray fluorescence spectrometry.[5] Blood samples were collected prior to administration of halothane and then 24 h, 48 h, and 6 days after anesthesia. Biotransformation of enflurane was assessed by determination of serum inorganic fluoride concentrations measured with an Orion® ion-specific fluoride electrode and an Orion® Model 701 digital *p*H/mv meter.[6] Blood samples were collected prior to administration of enflurane and then 1, 2, 5, and 10–12 h after the end of anesthesia. For both determinations, serum was separated immediately after clot retraction and kept frozen at −18° C until subsequent analysis. The amounts of inspired halothane and enflurane were expressed in MAC-hours for all groups (table 2). Postoperative hepatic function was assessed in all patients by measurement of aspartate animotransferase (SGOT) and alanine aminotransferase (SGPT) levels 24 h after anesthesia.

TABLE 2. Delivered Doses of Halogenated Anesthetics, MAC-hours (Mean ± SD)

	Halothane	Enflurane
Group 1 (n = 14)	2.5 ± 0.7 (n = 5)	3.5 ± 1.3 (n = 9)
Group 2 (n = 19)	3.5 ± 0.9 (n = 11)	4.4 ± 1.4 (n = 8)
Group 3 (n = 7)	3.4 ± 0.7 (n = 4)	2.5 ± 0.6 (n = 3)

Analysis of variance was used to compare preoperative plasma bromide (halothane) and fluoride (enflurane) concentrations among the three groups. Repeated measures analysis of variance followed by *t* tests were used to detect differences among preoperative and postoperative values within each group. To compare the amounts of anesthetic that were metabolized by the three groups of patients, the serum bromide and fluoride concentrations measured at different times were divided by the delivered dose of halothane or enflurane expressed in MAC-hours. This is a legitimate transformation, as the metabolism of halogenated anesthetics is linear in the MAC-hour range encountered in this study.[7] Analysis of variance was used for comparison of means and *t* tests when a difference was found. $P < 0.05$ was considered significant.

RESULTS

Mean values (±SD) of serum bromide and fluoride concentrations for each group are shown in tables 3*A* and 3*B*. Preoperative values were no different among the three groups of patients, but significant increases above control values were seen at each subsequent time interval.

Variations in serum bromide and fluoride concentration per MAC-hour for each group of patients are presented in figures 1 and 2. At each interval, significantly higher serum bromide and fluoride concentrations were found in patients undergoing removal of toxic thyroid adenoma (group 3) compared with levels in patients with treated Graves' disease (group 2); biotransformation was intermediate in control patients (group 1). The differences between control and untreated hyperthyroid patients were significant at each time interval after enflurane administration, but only at the first postoperative day after halothane administration. No significant differences between control patients and those suffering from Graves' disease were found after halothane administration. By contrast, significantly lower plasma fluoride concentrations were observed 1 and 2 h following enflurane administration in patients with Graves' disease compared

TABLE 3A. Serum Bromide Concentration (μM) in Patients Anesthetized with Halothane (Mean ± SD)

	Preanesthesia	24 h	48 h	6 days
Group 1 (n = 5)	64 ± 26	428 ± 129*	556 ± 125*	526 ± 101*
Group 2 (n = 11)	76 ± 52	620 ± 199*	705 ± 241*	654 ± 243*
Group 3 (n = 3)	66 ± 53	770 ± 160*	910 ± 199*	845 ± 173*

* Significantly different from preoperative values, $P < 0.001$.

TABLE 3B. Serum Fluoride Concentration (μM) in Patients Anesthetized with Enflurane (Mean ± SD)

	Preanesthesia	1 h	2 h	5 h	10–12 h
Group 1 (n = 9)	2.9 ± 0.8	12.9 ± 3.0*	13.1 ± 5.3*	10.1 ± 4.2*	7.3 ± 2.4*
Group 2 (n = 8)	2.3 ± 0.3	10.3 ± 2.5*	10.8 ± 3.3*	9.7 ± 2.1*	7.1 ± 1.5*
Group 3 (n = 4)	3.0 ± 0.9	13.1 ± 2.5*	12.0 ± 3.1*	9.8 ± 2.2*	7.8 ± 1.6*

* Significantly different from preoperative values; $P < 0.001$.

with control subjects. In all patients, postoperative SGOT and SGPT levels were within normal limits (table 4), with no single value exceeding 36 IU.

DISCUSSION

This study demonstrates that hyperthyroid patients metabolize more halothane and enflurane than do euthyroid patients as evidenced by higher plasma bromide and fluoride concentrations per MAC-hour of anesthesia. (In all cases, plasma fluoride and bromide concentrations remained below toxic values.[7–9]) The results are in agreement with those from previous studies of the metabolism of several nonanesthetic substrates, which suggested that hyperthyroidism leads to induction of the heptic microsomal enzyme system.[10] By contrast, no major differences in postoperative plasma bromide and fluoride levels per MAC-hour were found between euthyroid patients and those patients with treated Graves' disease. The latter, in fact, had the lowest mean metabolite values at all time periods (figs. 1 and 2).

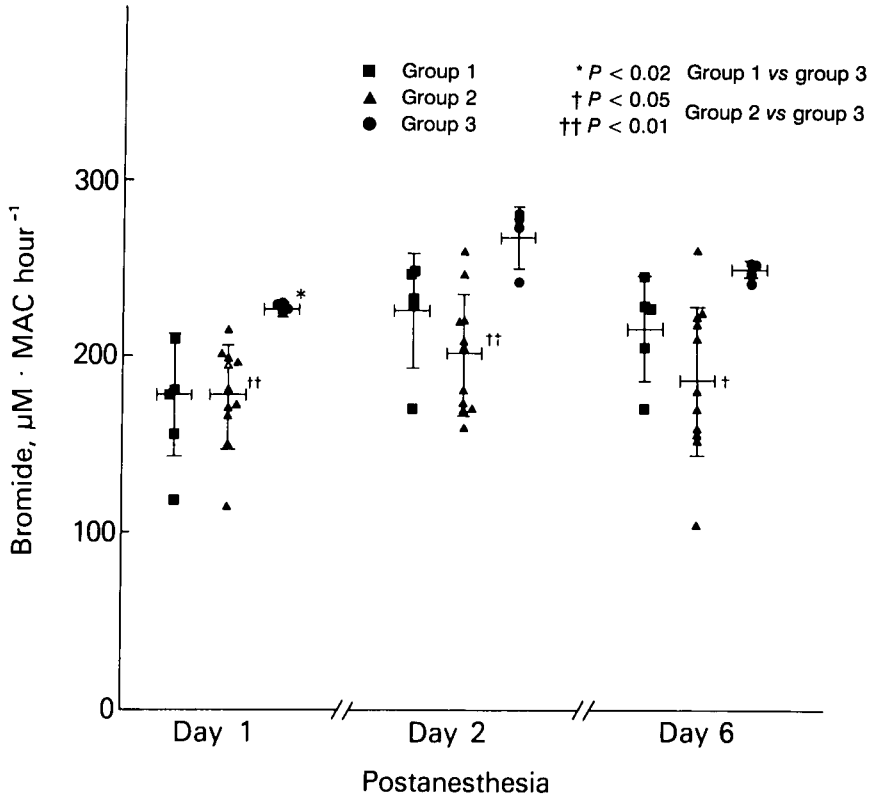

FIG. 1. Individual patient and group mean (±SD) serum bromide MAC·hour^{-1} of halothane anesthesia on days 1, 2, and 6 postanesthesia. Subjects with untreated toxic thyroid adenoma (group 3) generally had the highest values, whereas those with treated Graves' disease (group 2) had the lowest values. Statistical significances are shown in the key.

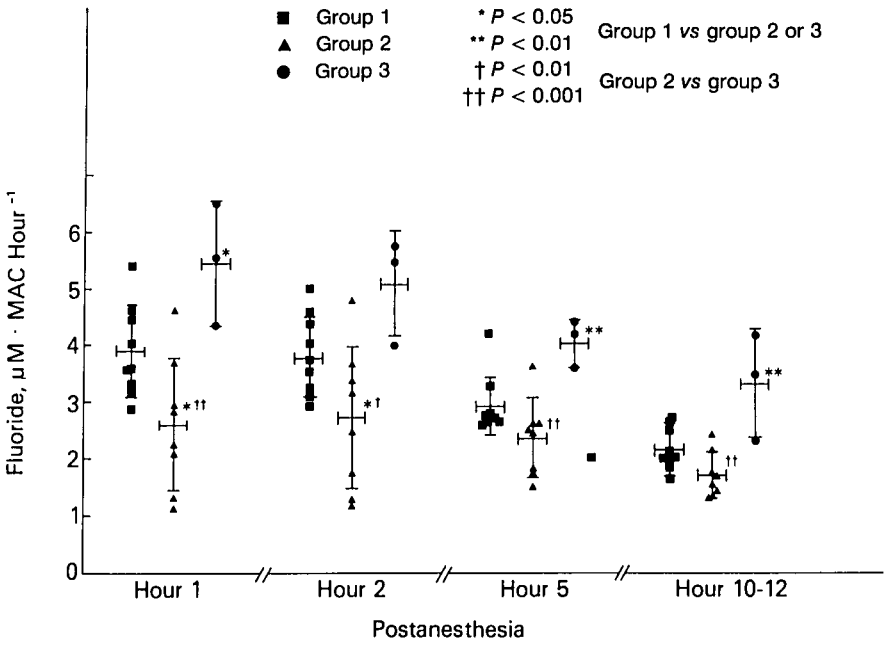

FIG. 2. Individual patient and group mean (±SD) serum fluoride MAC·hour^{-1} of enflurane anesthesia at 1, 2, 5, and 10–12 h postanesthesia. Subjects with untreated toxic thyroid adenoma (group 3) had the highest values, whereas those with treated Graves' disease (group 2) had the lowest values. Statistical significances are shown in the key.

One might question the use of serum bromide and fluoride measurements on the grounds that they would not detect all evidence of halothane and enflurane metabolism. In fact, both are suitable for the purpose. Serum bromide is a relatively good indicator of halothane biotransformation because it is released during both oxidative and reductive metabolism. However, one compound, 2-bromo-2-chloro-1,1-difluoroethylene, found in very small quantities in the expired air of patients anesthetized with halothane using a semiclosed or closed circuit, would not be detected by measurement of serum bromide. This compound, rather than being a product of halothane biotransformation, is probably a halothane decomposition product, formed as a result of the reaction of halothane with soda lime.[11] Thus, measurement of serum bromide should reflect all of the metabolism of halothane. The metabolism of enflurane involves an initial dechlorination reaction.[12] The product, 1,1-difluoromethoxy-1,1-difluoroacetylfluoride, is unstable and is defluorinated with the formation of 1,1-difluoromethoxy-1,1-difluoroacetic acid.[12] Thus, serum fluoride measurements should accurately reflect enflurane biotransformation.

TABLE 4. Transaminase Values* (Mean ± SD) 24 h after Operation

Groups	SGOT	SGPT
Group 1		
HAL (n = 5)	26.0 ± 9.1	20.8 ± 8.7
ENF (n = 9)	18.4 ± 5.5	22.2 ± 7.6
Group 2		
HAL (n = 11)	16.5 ± 4.5	16.3 ± 4.1
ENF (n = 8)	16.5 ± 4.8	16.5 ± 3.8
Group 3		
HAL (n = 4)	17.8 ± 2.2	19.0 ± 5.0
ENF (n = 3)	26.7 ± 9.5	25.3 ± 7.0

SGOT = aspartate aminotransferase; SGPT = alanine aminotransferase; HAL = halothane; ENF = enflurane.
* Normal Values, <40 IU.

The results also suggest that complex drug interactions affect metabolism of the halogenated anesthetics in patients treated with combinations of drugs such as phenobarbital, propranolol, and carbimazole, all of which are known to affect hepatic drug biotransformation. Phenobarbital stimulates the hepatic microsomal mixed-function oxidase system, consistently enhancing the biotransformation of all of the potent halogenated anesthetics except enflurane.[13–16] To the contrary, propranolol, by binding to cytochrome P-450,[17,18] inhibits the metabolism of numerous drugs, including theophylline and antipyrine.[19,20] Propranolol also may inhibit drug metabolism by causing a decrease in hepatic blood flow. However, phenobarbital may antagonize the effects of propranolol by enhancing its protein binding.[21] In one study, after 3 weeks of phenobarbital therapy the percentage of unbound propranolol fell from 15.2 ± 1.2 to 2.4 ± 0.3, accompanied by a reduction in beta-adrenergic blocking activity.[22] Antithyroid agents, such as propylthiouracil, interfere with hepatic biotransformation as they inhibit hepatic microsomal enzymes.[23] In animal experiments, propylthiouracil protects against liver damage in the ethanol-hypoxia model[24] and also injury produced by carbon tetrachloride[25] and acetaminophen,[26] although the mechanism of protection appears to be independent of its action on hepatic drug metabolism.[25,26] Carbimazole, the antithyroid drug used

in this study, is not believed to have extrathyroid actions.[27] However, through the action of its active metabolite, methimazole, carbimazole might decrease hepatic metabolism indirectly by lowering plasma T_3 and T_4 concentrations.

We conclude that in patients with Graves' disease, those drugs that inhibit drug metabolism have a more prevalent effect than those that cause stimulation. The clinical implications of these findings are unknown. If liver damage is caused by hepatotoxic metabolites of the halogenated anesthetics, treated hyperthyroid patients might be somewhat protected. On the other hand, because propranolol reduces hepatic blood flow, its use could enhance detrimental anaerobic conditions in heptic centrilobular cells. At the present time, more definitive statements cannot be made.

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