then chest tubes. Ideally, ventilation should be spontaneous before decompression of the tension pneumothorax. Positive airway pressure and controlled ventilation can increase the pneumothorax, resulting in cardiovascular collapse. Recovery room personnel must be alert and prepared to initiate immediate therapy.

The author thanks Dr. Thomas P. Keon for his editorial assistance.

REFERENCES

1. Ganfield RA, Chapin JW: Pneumothorax with upper airway laser surgery. ANESTHESIOLOGY 56:398–399, 1982
2. Snow JC, Norton ML, Saluja TS, Estanislao AF: Fire hazard during CO2 laser microsurgery on the larynx and trachea. Anesth Analg 55:146–147, 1976
3. Hirschman CA, Smith J: Indirect ignition of the endotracheal tube during carbon dioxide laser surgery. Arch Otolaryngol 106: 639–641, 1980
4. Leibowitz HM, Peacock GR: Corneal injury produced by carbon dioxide laser surgery. Arch Otolaryngol 81:713–721, 1969
5. Davis RK, Simpson GT: Safety with the carbon dioxide laser. Otolaryngol Clin North Am 16:801–813, 1983
6. Snow JC, Kripke BJ, Strong MS, Jako GJ, Meyer MR, Vaughan CW: Anesthesia for carbon dioxide laser microsurgery on the larynx and trachea. Anesth Analg 53:507–512, 1974
7. Birch AA: Anesthetic considerations during laser surgery. Anesth Analg 52:53–58, 1973
8. Hermens JM, Bennett MJ, Hirshman CA: Anesthesia for laser surgery. Anesth Analg 62:218–229, 1983
9. Healy GB, Strong MS, Shapshay S, Vaughan C, Jako G: Complications of CO_2 laser surgery of the aerodigestive tract: Experience of 4416 cases. Otolaryngol Head Neck Surg 92:13–18, 1984

Anesthesiology
64:122–125, 1986

Postoperative Hepatic Dysfunction after Halothane or Enflurane Anesthesia in Patients with Hyperthyroidism

HIDEKO SEINO, M.D.,* SHUJI DOHI, M.D.,† YUJI AIYOSHI, M.D.,‡ TARO MIZUTANI, M.D.,§ KOUICHI NAKAMURA, M.D.,§ HIROSHI NAITO, M.D.¶

Increasing experimental evidence indicates that the hyperthyroid state enhances hepatotoxicity by volatile anesthetic agents in rodents.[1–4] The incidence of liver lesion after exposure to halothane in hyperthyroid rats is approximately four times more than that after enflurane or isoflurane.[2] Patients with hyperthyroidism usually come to anesthesia and surgery in an euthyroid state by taking antithyroid drugs. Perhaps the hypermetabolic state of the liver in such patients has not returned to normal by antithyroid drugs. In addition, antithyroid drugs can be hepatotoxic.[5,6] Thus, patients with hyperthyroidism, even in an euthyroid state, could have a significant risk of developing postoperative hepatic dysfunction when they are anesthetized by inhaled anesthetics, especially halothane.[7,8]

We, therefore, retrospectively investigated whether there is a higher incidence of early postoperative hepatic dysfunction in patients with hyperthyroidism when compared with patients with nonfunctional thyroid tumors. Second, we sought to determine whether halothane is more likely to produce hepatic dysfunction in patients with hyperthyroidism when compared with enflurane following thyroid surgery.

MATERIALS AND METHODS

From September 1980 to August 1984, 183 patients underwent elective thyroid surgery for both hyperthyroidism and nonfunctional thyroid tumors. Of these, 66 patients had hyperthyroidism, and the remaining had nonfunctional thyroid tumor (simple or nodular goiter, carcinoma, adenoma). Halothane was used in 78 patients (31 with hyperthyroidism and 47 with normal thyroid function), and enflurane was used in 105 patients (35 with hyperthyroidism and 70 with normal thyroid function) (table 1).

All patients with hyperthyroidism had been rendered euthyroid by use of antithyroid drugs (propylthiouracil or methimazole, Lugol's solution, or a combination of propylthiouracil and Lugol's solution). In some of these patients, a hyperkinetic circulatory status was controlled with oral propranolol in doses of 30–60 mg/day (12 pa-

* Chief Resident, Department of Anesthesiology.
† Associate Professor of Anesthesiology, Institute of Clinical Medicine.
‡ Associate Professor and Chief of Endocrinological Surgery.
§ Assistant Professor, Department of Anesthesiology.
¶ Professor and Chairman, Department of Anesthesiology.

Received from the Departments of Anesthesiology and Endocrinological Surgery, Institute of Clinical Medicine, University of Tsukuba, Sakuramura, Ibaraki 305, Japan. Accepted for publication August 26, 1985.

Address reprint request to Dr. Dohi.

Key words: Anesthetics, volatile: halothane; enflurane. Hormones: thyroid. Liver: hepatoxicity.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/64/1/122/310884/0000542-198601000-00025.pdf by guest on 23 January 2022

TABLE 1. Results of Operative Characteristics in the Four Groups of Patients

	Hyperthyroidism		Normal Thyroid Function	
	Enflurane	Halothane	Enflurane	Halothane
Number of patients	35	31	70	47
Sex (M/F)	10/25	9/22	10/60	5/42
Age (yr)	33 ± 12*	34 ± 9.2*	48 ± 13	46 ± 13
Body weight (kg)	54 ± 9	57 ± 8	55 ± 7	55 ± 10
Duration of operation (h)	3.8 ± 0.8†	3.2 ± 1.2	3.6 ± 1.0†	2.8 ± 0.9
Duration of anesthesia (h)	4.7 ± 0.9†	3.9 ± 1.2	4.5 ± 1.1†	3.7 ± 1.0
Preanesthetic systolic BP (mmHg)	122 ± 12	125 ± 10	123 ± 13	122 ± 15
Intraoperative systolic BP min‡ (mmHg)	93 ± 9†	101 ± 14	92 ± 12†	100 ± 12
Intraoperative blood loss (ml)	231 ± 126*	226 ± 100*	155 ± 140	94 ± 62
Intraoperative BT max (°C)§	37.1 ± 0.5	37.1 ± 0.7	37.2 ± 0.7	37.1 ± 0.5

* $P < 0.01$ *versus* normal thyroid function. Each number indicates mean ± 1 SD.

† $P < 0.05$ *versus* halothane.

‡ Indicates minimum systolic arterial blood pressure recorded during anesthesia.

§ Indicates maximum rectal body temperature recorded during anesthesia.

tients in the halothane group, 12 in the enflurane group). There were wide individual variations of the duration from initial diagnosis of hyperthyroidism to surgery (1–13 yr). The duration of euthyroid status before surgery also varied individually. Antithyroid drugs were reduced or discontinued preoperatively.

The anesthesia record of each patient was reviewed. In our institution, anesthetic techniques and drugs used for thyroid surgery were virtually identical for this study period. Preoperative medication consisted of hydroxyzine 100 mg im, or diazepam 100 mg po, 1 h before arrival in the operating room without anticholinergic drugs. In the operating room, after the establishment of iv and ECG monitors and measurements of heart rate and arterial blood pressure, general anesthesia was induced with thiamylal 4.0–5.0 mg/kg, iv, and succinylcholine chloride 1.0 mg/kg, iv, was given to facilitate tracheal intubation. For patients with hyperthyroidism, halothane or enflurane was combined with N_2O before the tracheal intubation. For all patients, anesthesia was maintained with halothane (inspired concentration 0.7–1.5%) or enflurane (1.0–2.3%), N_2O (66%), and O_2 (33%).

Routine laboratory examinations including complete blood counts and serum chemical constituents such as glutamic–oxaloacetic transaminase (SGOT), glutamic–pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) were performed at postoperative day 1 or 2 (in some patients) and repeated on postoperative day 6 or 7. One patient who developed myoglobinemia, elevated SGOT and SGPT, and an increase in creatine phosphokinase (20770 mU/ml) after enflurane, N_2O, O_2, and succinylcholine chloride was excluded from the results.

Statistical analysis was performed by analysis of variance, then by Student's *t* test for paired or unpaired values. *P* values of less than 0.05 were considered significant. All values are expressed as mean ± 1 SD. We used the chi-square analysis on a 2 × 2 table for comparison of numbers of patients in whom SGOT, SGPT, and lactate dehydrogenase (LDH) increased more than 2 SDs of each mean of the preoperative values.

RESULTS

There were no significant differences in the duration of anesthesia time, preanesthetic values of systolic blood pressure and heart rate, and highest rectal temperature during anesthesia among the four groups of patients (table 1). The mean values of lowest arterial blood pressure in the enflurane groups were lower than those in the halothane groups in both patients with hyperthyroidism and those with normal thyroid function (table 1). The patients with hyperthyroidism were significantly younger than those with normal thyroid function ($P < 0.01$). Mean volumes of intraoperative blood loss were larger in patients with hyperthyroidism than in those with normal thyroid function ($P < 0.01$). However, there was no significant difference in any of these values, except duration of surgery, between the patients given enflurane and those given halothane in each group of hyperthyroidism or normal thyroid function (table 1). Only one patient had a previous history of hepatic disease. No patient had previously received a halogenated anesthetic.

Preoperatively, none of the patients had hepatic dysfunction in any of the four groups. Preoperative values of hemoglobin (Hb), SGOT, and SGPT (measured by the ultraviolet method) indicated no significant difference among the four groups of patients. The mean values of LDH (measured by the ultraviolet method) were somewhat larger in the enflurane group than in the halothane group, although there was no patient with an abnormally

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/64/1/122/310884/0000542-198601000-00025.pdf by guest on 23 January 2022

TABLE 2. Values of Preoperative Laboratory Examinations in the Four Groups of Patients

	Hyperthyroidism		Normal Thyroid Function	
	Enflurane (n = 35)	Halothane (n = 31)	Enflurane (n = 70)	Halothane (n = 47)
Hemoglobin (g/100 ml)	14.1 ± 1.5	13.7 ± 1.6	13.3 ± 1.1	13.3 ± 1.1
SGOT (8–40 U)	13 ± 5	14 ± 5	13 ± 5	13 ± 7
SGPT (5–35 U)	10 ± 8	11 ± 7	11 ± 7	9 ± 6
LDH (50–400 U)	276 ± 49*	229 ± 36	297 ± 56*	266 ± 53
A_1-phosphatase (5–13 U)	11 ± 8†	11 ± 6†	6 ± 2	4 ± 2
Triiodothyronine (T_3) (100–190 ng/ml)	140 ± 50	130 ± 45	118 ± 18	128 ± 19
Thyroxine (T_4) (5–13.7 μg/ml)	4.9 ± 3.5†	5.7 ± 3.2†	7.8 ± 1.7	8.3 ± 1.8
Resin triiodothyronine uptake (RT_3U) (25–35%)	27.8 ± 2.5	28.8 ± 5.4	28.8 ± 2.1	28.7 ± 2.5

Values in parentheses indicate normal ranges.
Each number indicates mean ± 1 SD.
* $P < 0.01$ *versus* halothane.
† $P < 0.05$ *versus* normal thyroid function.

high value of LDH. Plasma levels of alkaline phosphatase were also higher in patients with hyperthyroidism than those with normal thyroid function. Neither serum triiodothyronine (T_3), thyroxine (T_4), nor resin triiodothyronine uptake (RT_3U) differed between the patients given enflurane and those given halothane (table 2), although the mean values of T_4 in the patients with hyperthyroidism were lower than in those with normal thyroid function ($P < 0.05$).

No patient developed clinically significant hepatic dysfunction in the early postoperative period. The mean values of SGOT increased significantly, although within normal ranges, on day 1 in both the halothane groups and the enflurane group with normal thyroid function. SGPT did not increase significantly in any of the groups of patients. The mean values of LDH in patients with hyperthyroidism anesthetized with halothane increased postoperatively ($P < 0.05$, table 3).

Table 4 shows numbers of patients in which SGOT, SGPT, and LDH at postoperative day 1 increased more than the values of 2 SDs of each mean of the preoperative values. In both groups of patients with hyperthyroidism, there was a significantly higher incidence of increased LDH ($P < 0.01$).

TABLE 3. Postoperative Day 1 and 7 Changes of SGOT, SGPT, and LDH in the Four Groups of Patients

	Hyperthyroidism		Normal Thyroid Function	
	Enflurane	Halothane	Enflurane	Halothane
SGOT				
1	21 ± 31	21 ± 8*	17 ± 5*	20 ± 13*
7	13 ± 7	14 ± 6	13 ± 4	18 ± 18
SGPT				
1	8 ± 7	12 ± 7	10 ± 7	9 ± 7
7	9 ± 7	10 ± 6	10 ± 6	14 ± 23
LDH				
1	297 ± 56	274 ± 136*	299 ± 53	271 ± 58
7	287 ± 41	252 ± 45*	290 ± 51	280 ± 70

* Statistically significant change from preoperative values of table 2 ($P < 0.05$).

There were three female patients in halothane groups who developed moderate hepatic dysfunction (SGOT and SGPT were increased more than 100 U) after the observation periods of the study. Increased SGOT and SGPT were found at postoperative day 7 in one patient and at postoperative day 12 and 13 in the other two. These high values of SGOT and SGPT returned to control within 2 weeks in all three patients.

DISCUSSION

The aim of the present study was to evaluate whether patients with hyperthyroidism have a higher anesthetic risk of postoperative hepatic dysfunction. Because the surgical field rather than the specific anesthetic drug has been thought to be the important determinant of postoperative hepatocellular dysfunction,[9,10] we retrospectively compared hepatic function following thyroid surgery between patients with hyperthyroidism and those with normal thyroid function. There were some differences in age, gender distributions, and operative blood loss between the two groups, but other factors that may contribute to postoperative hepatic dysfunction, such as preexisting hepatic disease, nutritional status, repeated surgery, blood transfusion, sepsis, hypotension, and duration of operation were either absent or similarly present in both groups. The existing differences are unlikely to be important factors contributing to the higher incidences

TABLE 4. Numbers of Patients in which SGOT, SGPT, and LDH at Postoperative Day 1 Increased more than 2 SD of Each Mean Value of the Preoperative Values

	SGOT	SGPT	LDH
Hyperthyroid	13/56	1/56	7/56*
Enflurane	5/30	0/30	2/30*
Halothane	8/26	1/26	5/26*
Normal thyroid function	11/95	1/95	0/97
Enflurane	3/56	1/56	0/58
Halothane	8/39	0/39	0/39

* $P < 0.01$ *versus* normal thyroid function.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/64/1/122/310884/0000542-198601000-00025.pdf by guest on 23 January 2022

of the increased LDH in the hyperthyroid patients; rather, they may indicate some of the limitations of a retrospective study. Although increasing experimental evidence indicates that hyperthyroid status may enhance postoperative hepatic dysfunction, the results of our study show that patients with hyperthyroidism are unlikely to have a higher incidence of early postoperative hepatic dysfunction.

Experimentally, Wood *et al.*[1] and Berman *et al.*[2] reported that exposure of T_3-pretreated rats to 1.8% enflurane and 1% halothane in 21% O_2 (air) for 2 h resulted in hepatic centrilobular necrosis, and the incidence of the liver lesion was 24% and 92% with enflurane and halothane, respectively. They speculated that anesthetic-induced hepatotoxicity observed in hyperthyroid rats may be related to hypoxic damage to hypermetabolic centrilobular cells resulting from anesthetic-induced depression of splanchnic blood flow.[11] Because the hepatic lesions and elevated SGPT that appeared immediately after halothane exposure were related to the dose of T_3 (plasma concentration of T_3 being 863–30,000 ng/100 ml),[1] no significant changes of SGPT in the hyperthyroid patients anesthetized with halothane in our study may be attributable to the well-controlled state of disease in the patients in whom serum T_3 ranged from 98 to 180 ng/ml.

In patients with hyperthyroidism, drug-related hepatotoxicity occurs almost exclusively with propylthiouracil, whereas cholestatic jaundice has been typically associated with methimazole.[7] In our study, there was no patient who had a clinically obvious hepatic dysfunction preoperatively or postoperatively. Thyroxine has been shown to enhance the hepatic damage caused by carbon tetrachloride;[12] however, in the same experimental model, propylthiouracil and thyroidectomy protect against development of hepatic damage.[12,13] Perhaps propranolol, given in most patients with hyperthyroidism, might have had some beneficial effects on O_2 consumption and splanchnic blood flow,[14] which could be reduced by halothane and enflurane.[15]

The reason for the increased SGOT, although within normal ranges, in the halothane groups and enflurane–normal-thyroid-function group cannot be determined from our study. Because there was no significant increase in SGPT, the slight increase of SGOT may be related to muscle damage from surgery[9,16,17] or succinylcholine–induced fasciculation rather than hepatic damage *per se.* Because there was significantly shorter duration of surgery and, thus, anesthesic exposure in the halothane groups as compared with the enflurane groups, it is unwise to discuss differences in anesthetic effects of each agent on postoperative hepatic dysfunction, although duration of operation does not seem to affect postoperative increases of LDH_5 isozyme fraction.[10]

Anesthesia for patients with hyperthyroidism is based on patients being euthyroid with antithyroid drugs and the hyperkinetic circulation controlled with propranolol.[18] Our results indicate that patients with hyperthyroidism are not likely to have a higher risk of postoperative hepatic dysfunction. However, a significantly higher incidence of elevated LDH at postoperative day 1 following both halothane and enflurane in patients with hyperthyroidism deserves a prospective study using more sensitive and specific examinations, such as LDH_4 or LDH_5 isozyme fraction, for hepatocellular injury.

References

1. Wood M, Berman ML, Harbison RD, Hoyle P, Phythyon JM, Wood AJJ: Halothane-induced hepatic necrosis in triiodothyronine-pretreated rats. ANESTHESIOLOGY 52:470–476, 1980
2. Berman ML, Kuhnert L, Phythyon JM, Holaday DA: Isoflurane and enflurane-induced hepatic necrosis in triiodothyronine-pretreated rats. ANESTHESIOLOGY 58:1–5, 1983
3. Holaday DA, Berman ML, England R, Abumrad N: The effect of halothane on metabolic pathways in the hyperthyroid rat (abstract). ANESTHESIOLOGY 61:A266, 1984
4. Berman ML, Kuhnert L, Phythyon JM, Holaday DA: Lack of gender effect of triiodothyronine enhancement of halothane induced hepatotoxicity (abstract). ANESTHESIOLOGY 61:A275, 1984
5. Ashkar FS, Miller R, Smoak WM III, Gilson AJ: Liver disease in hyperthyroidism. South Med J 64:462–465, 1971
6. Cooper DS: Antithyroid drugs. N Engl J Med 311:1353–1362, 1984
7. Smith AC, Berman ML, James RC, Harbison RD: Characterization of hyperthyroidism enhancement of halothane-induced hepatotoxicity. Biochem Pharmacol 32:3531–3539, 1983
8. Uetrecht J, Wood AJJ, Phythyon JM, Wood M: Contrasting effects on halothane hepatotoxicity in the phenobarbital hypoxia and triiodothyronine model: Mechanistic implications. ANESTHESIOLOGY 59:196–201, 1983
9. Clarke RSJ, Doggart JR, Lavery T: Changes in liver function after different types of surgery. Br J Anaesth 48:119–128, 1976.
10. Viegas O, Stoelting RK: LDH_5 changes after cholecystectomy or hysterectomy in patients receiving halothane, enflurane, or fentanyl. ANESTHESIOLOGY 51:556–558, 1979
11. Berman ML, Kuhnert L, Phythyon JM, Holaday DA: Mechanism of liver necrosis in hyperthyroid rats. (Correspondence in reply). ANESTHESIOLOGY 59:591–592, 1983
12. Calvert DN, Brody TM: The effects of thyroid function upon carbon tetrachloride hepatotoxicity. J Pharmacol Exp Ther 134:304–310, 1961
13. Orrego H, Carmichael FJ, Phillips MJ, Kalant H, Khanna J, Israel Y: Protection by propylthiouracil against carbon tetrachloride-induced liver damage. Gastroenterology 71:821–826, 1976
14. Price HL, Cooperman LH, Warden JG: Control of the splanchnic circulation in man. Role of beta-adrenergic receptors. Circ Res 21:333–340, 1967
15. Andreen M: Inhalation versus intravenous anaesthesia. Effects on the hepatic and splanchnic circulation. Acta Anaesthesiol Scand [Suppl] 75:25–31, 1982
16. McEwan J: Liver function tests following anaesthesia. Br J Anaesth 48:1065–1069, 1976
17. Neuberger J, Williams R: Halothane anaesthesia and liver damage. Br Med J 289:1136–1139, 1984
18. Tasch MD: Endocrine diseases, Anesthesia and Co-existing Disease. Edited by Stoelting RK, Dierdorf SF. New York, Churchill Livingstone, 1983, pp 437–483

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/64/1/122/310884/0000542-198601000-00025.pdf by guest on 23 January 2022