COMPARATIVE TOXICITY OF ISOFLURANE, HALOTHANE, FLUROXENE AND DIETHYL ETHER IN HUMAN VOLUNTEERS

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INTRODUCTION

ALTHOUGH SEVERAL STUDIES have examined the hepatorenal injury that may occur in man following exposure to anaesthetic drugs, most are tainted by the presence of other medications, the concomitant stress imposed by the operation or the prior existence of hepatic or renal disease. Other studies have failed to measure anaesthetic dose (alveolar or arterial concentrations) and the duration of anaesthetic exposure, although such measurements are necessary to quantitate the imposed time-dose stress.

During our studies of the effects of various anaesthetics on cardiorespiratory function[1–7] we also evaluated the effects of these anaesthetics on subsequent hepatic and renal function. These measurements were made in healthy, young human volunteers and were uncomplicated by prior medication or concomitant operation. Anaesthesia was prolonged and at times profound. We present the results of the hepatic, renal and haematological studies in the following report. The findings suggest that small but significant differences exist among anaesthetics in their abilities to produce adverse effects. However, the changes seen were minimal, even with those agents which caused abnormalities.

METHODS

Many of the details of the methods used in this study have been described previously and only additions or deviations from prior protocols will be noted.[1–7] Briefly, studies were made on healthy volunteers between 21 and 30 years of age. Blood and voided urine specimens were obtained immediately prior to anaesthesia. Anaesthesia was induced and maintained only with the agent under study which was isoflurane or halothane with or without nitrous oxide (70 per cent), fluroxene or diethyl ether (Table I). Anaesthetic concentrations as multiples of the minimal alveolar concentration (MAC) were altered according to the needs of the circulatory or respiratory studies. One group receiving isoflurane and oxygen was made hypercapnoeic (isoflurane-CO_2) and one was not. The group receiving halothane

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Supported by Ohio Medical Products, Division of Air Reduction Co., Inc. and in part by grants 5T1 GM0063-11, 12 and 1PO1GM15571-O1A1, 02.

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TABLE I

DURATION OF ANAESTHESIA AND TIME-DOSE FACTORS OF ANAESTHETIC EXPOSURE FOR EACH GROUP.

The time-dose factor was derived by multiplying the alveolar anaesthetic concentration by the duration (in hours) of exposure to that concentration and dividing by MAC. The time-dose segments for each volunteer were summed and from results for all volunteers in each group mean values ± standard error were computed

	Number of Volunteers	MAC*	Minutes of Anaesthesia	Time-Dose Factor
Isoflurane-O_2	7	1.3[11]	390 ± 11	8.4 ± 0.4
Isoflurane-CO_2	10	1.3[11]	320 ± 11	6.4 ± 0.2
Isoflurane-nitrous oxide†	9	1.3[8,11]	387 ± 4	11.3 ± 0.2
Halothane-CO_2	8	0.84[8]	421 ± 8	10.1 ± 0.5
Halothane-nitrous oxide	9	0.84[8]	437 ± 14	13.2 ± 0.6
Fluroxene	11	3.76[10]	358 ± 31	15.2 ± 0.8
Diethyl ether	10	2.12[9]	398 ± 24	13.6 ± 0.8

*MAC = per cent of 1 atmosphere, adjusted for subjects' ages.[12]
†For nitrous oxide contribution to MAC, see text.

in oxygen was also subjected to hypercapnia (halothane-carbon dioxide). In these two groups, hypercapnia resulted from maintenance of spontaneous respiration and from imposed increases in P_{CO_2} to perform CO_2 response tests. Subjects were hypercapnoeic throughout the study but the range of abnormality varied. At the deepest level of isoflurane anaesthesia, $PaCO_2$ averaged 64.7 torr; during halothane it was 60.6 torr. The maximum $PaCO_2$ achieved during CO_2 challenges was between 80 and 90 torr. A time-dose factor which combined two variables which may influence toxicity, duration and depth of anaesthesia, was derived for each anaesthetic group (Table I). This was obtained by multiplying the alveolar concentration by the duration of exposure to that concentration and then dividing by the MAC for each anaesthetic.[8–11] In these calculations we assumed that 70 per cent nitrous oxide equalled 0.45 per cent halothane and 0.75 per cent isoflurane.[10] An additional correction was made for the influence of age on MAC.[12] Analysis of several such time-dose segments for each volunteer was necessary since one dose was not maintained for the entire duration of anaesthesia. All such segments for any one volunteer were added together. The mean values for all volunteers in each group were averaged to obtain the factors shown in Table I.

The total volume of fluid administered intravenously during the period of study ranged from 2000–3000 ml and consisted of lactated Ringers' solution and 5 per cent dextrose in water to which 22 mEq sodium bicarbonate had been added. The volunteers were kept fasting until the morning after the study but during this recovery period they received an infusion of 5 per cent dextrose in water at a rate of 100 ml per hour. Blood and voided urine specimens were obtained the morning following anaesthesia and again seven days after anaesthesia in all volunteers. Blood samples were taken from some volunteers at other times as noted in the tables.

Bromsulphthalein (BSP) was measured as per cent retention 45 minutes after injection of a 5 mg/kg dose. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine, total serum protein, serum albumin, serum potassium, sodium, chloride, glucose, and bicar-

bonate content were measured as described by Smolelis and Hartsell.[13] The rationale for lysozyme analysis was an increase in urinary lysozyme without a concomitant increase in plasma lysozymes would suggest cellular disruption in the genitourinary tract. Haematocrit determinations, leukocyte and differential cell counts and platelet counts were made. Not all analyses were performed in each anaesthetic group. In general, as these studies progressed, the evaluation became more comprehensive and included more analyses.

Measurements of serum inorganic fluoride were made in four volunteers in the group anaesthetized with isoflurane-nitrous oxide. Samples were drawn prior to anaesthesia, at the end of anaesthesia and one, three, or seven days after anaesthesia. The samples were centrifuged, the serum was extracted, frozen and later analyzed with a fluoride electrode.*

For intra-anaesthetic comparisons, t values were obtained by paired analyses. For inter-anaesthetic comparisons, t values were obtained by unpaired analyses. We accepted as significant any p value of less than 0.05. Mean values ± one standard error are presented.

RESULTS

Hepatic Function (Table II)

BSP increased significantly on the first post-anaesthesia day in the volunteers exposed to isoflurane-oxygen, halothane-carbon dioxide, halothane-nitrous oxide, and fluroxene, but not in the other groups. Increases in BSP retention were significantly greater in the halothane and fluroxene groups than in the isoflurane-oxygen group. Hypercapnia during isoflurane or halothane anaesthesia did not cause any greater increases in BSP than were observed at normocapnia when oxygen or nitrous oxide were administered with these agents. By the seventh day, only those volunteers who received halothane with carbon dioxide continued to have significantly high BSP values. Only fluroxene increased the mean SGOT value significantly on the first post-anaesthesia day. This value was still greater than the preanaesthetic value on day seven. No significant changes were observed in SGPT, LDH, serum cholesterol or alkaline phosphatase values except for decreases in serum cholesterol and alkaline phosphatase in the group receiving isoflurane-nitrous oxide at one and three days post-anaesthesia.

Renal Function (Table III)

Blood urea nitrogen (BUN) decreased significantly in all isoflurane groups and in the halothane-carbon dioxide and ether groups and had returned to control values by seven days in all but the isoflurane-carbon dioxide and isoflurane-nitrous oxide groups. Creatinine did not change significantly in any of the groups. Uric acid decreased significantly one day after isoflurane-carbon dioxide and isoflurane-nitrous oxide and increased significantly one day after halothane with carbon dioxide. Uric acid values were significantly higher the seventh day than the first day after isoflurane-oxygen. There were no significant changes in urine or plasma lysozyme levels nor were there significant differences among the groups. The urine pH tended to increase slightly and specific gravity to decrease on the first day

*Fluoride analyses were generously provided by Dr. Richard Mazze, Department of Anesthesiology, Stanford University School of Medicine, Palo Alto, Calif.

TABLE II

LIVER FUNCTION TEST RESULTS PRIOR TO AND FOLLOWING ANAESTHESIA.
Mean values ± standard error of the mean are shown

	N	Time	Bromsulphthalein (% Retention)	Serum Glutamic Oxaloacetic Transaminase (units)	Serum Glutamic pyruvic Transaminase (units)	Lactic Dehydro-Genase (units)	Alkaline Phosphatase (units)	Serum Cholesterol (mg%)
Isoflurane-O_2	7	p	2.9 ± 0.2	34.0 ± 1.0	13.8 ± 1.9(6)	146.0 ± 6.9	54.3 ± 7.9	209.9 ± 14.7
	7	1	5.8 ± 1.2*	48.0 ± 9.0	18.9 ± 4.5	153.6 ± 15.9	45.9 ± 7.0	212.9 ± 16.3
	7	7	2.9 ± 0.5	40.3 ± 4.8	14.1 ± 1.7	141.6 ± 5.3	48.0 ± 7.0	222.1 ± 18.7
Isoflurane-CO_2	10	p	3.1 ± 0.4(9)	35.9 ± 2.3	10.0 ± 0.6	148.6 ± 6.6	53.8 ± 6.4	213.3 ± 11.8
	10	1	5.0 ± 1.3(9)	44.2 ± 4.4	12.4 ± 1.9	148.1 ± 7.3	52.1 ± 4.8	203.3 ± 9.9
	10	7	4.2 ± 0.6(9)	37.9 ± 1.6	11.8 ± 1.1	144.4 ± 5.6	47.2 ± 5.1	204.6 ± 8.1
Isoflurane-N_2O	8	p	3.6 ± 0.3	48.1 ± 8.3	11.9 ± 3.0	161.3 ± 7.4	54.3 ± 5.7	195.8 ± 15.3
	8	1	4.9 ± 0.8	53.1 ± 5.5	10.4 ± 1.3	187.5 ± 19.5	52.2 ± 5.9	179.9 ± 11.5*
	8	3		46.4 ± 3.0		164.0 ± 9.4	42.0 ± 6.0	185.1 ± 10.6
	8	7	3.8 ± 0.5	39.4 ± 2.8	12.3 ± 2.2	166.8 ± 12.4	43.5 ± 4.5	178.4 ± 11.6
Halothane-CO_2	8	p	2.8 ± 0.3	29.9 ± 2.9	9.8 ± 1.5	144.3 ± 8.6(7)	59.1 ± 6.0(7)	186.9 ± 11.9(7)
	8	1	11.3 ± 2.2*	44.4 ± 10.2	11.8 ± 3.0	170.7 ± 29.9(6)	52.8 ± 7.3(6)	171.0 ± 11.4(6)
	8	7	5.7 ± 0.9(7)*	44.0 ± 8.7	17.4 ± 5.6	173.4 ± 18.0	51.0 ± 5.4	
Halothane-N_2O	8	p	2.5 ± 0.5	34.9 ± 10.2(7)	21.8 ± 7.7(7)			
	8	1	9.2 ± 2.2*	56.7 ± 13.0(6)	25.6 ± 8.4(6)			
	8	7	4.5 ± 1.4	41.1 ± 4.1(7)	19.4 ± 3.2(7)			
Fluroxene	10	p	2.3 ± 0.76(11)	18.4 ± 0.7	14.1 ± 1.8			
	10	1	7.7 ± 1.0(11)*	54.8 ± 9.1*	22.8 ± 4.0			
	10	7	1.6 ± 0.48(11)	25.5 ± 5.6*	18.2 ± 1.7			
Diethyl Ether	7	p	2.3 ± 0.4	23.9 ± 2.5	16.0 ± 2.1			
	7	1	10.3 ± 3.3	27.1 ± 5.3	22.9 ± 1.9*			
	7	7	4.1 ± 2.5(6)	23.2 ± 2.7(6)	20.7 ± 3.3(6)			

Time: p = prior to anaesthesia, 1, 3 and 7 days after anaesthesia.
N = number of subjects. Variation of N in certain groups is indicated ( ).
Normal values are: SGOT 5–40 units, SGPT 5–30 units, LDH 80–330 units, Alkaline phosphates 10–110 units, Cholesterol 110–300 mg%.
*Significantly different from control $p < 0.05$.

TABLE III

KIDNEY FUNCTION TEST RESULTS PRIOR TO AND FOLLOWING ANAESTHESIA.
Mean values ± 1 standard error of the mean are shown

	N	Time	Blood Urea Nitrogen	Serum Creatinine	Serum Uric Acid	Lysozyme	
						Urine	Plasma
Isoflurane-O_2	7	p	16.4 ± 1.7(6)	1.1 ± 0.04	4.97 ± 0.38	0.15 ± 0.08(6)	7.6 ± 1.6
	7	1	9.0 ± 0.6(6)*	1.1 ± 0.07	5.07 ± 0.45	0.25 ± 0.07(6)	8.6 ± 1.4
	7	7	15.9 ± 1.2(2)	1.1 ± 0.05	5.73 ± 0.51*	0.57 ± 0.11(7)	9.3 ± 2.1(6)
Isoflurane-CO_2	10	p	16.3 ± 0.7(8)	1.0 ± 0.04(5)	6.62 ± 0.35(8)	0.55 ± 0.14	6.5 ± 0.63(6)
	10	1	10.0 ± 1.2(8)*	1.1 ± 0.08(5)	5.85 ± 0.30(8)*	0.50 ± 0.10	7.17 ± 0.46(6)
	10	7	13.3 ± 1.3(8)*	1.2 ± 0.08(5)	6.81 ± 0.25(8)	0.59 ± 0.09(8)	7.83 ± 0.78(6)
Isoflurane-N_2O	8	p	16.5 ± 1.6	1.1 ± 0.00	5.86 ± 0.25		
	8	1	8.6 ± 0.7*	1.1 ± 0.00	5.21 ± 0.35*		
	8	3	13.4 ± 1.4*	1.1 ± 0.10	5.55 ± 0.44		
	8	7	14.9 ± 1.5	1.0 ± 0.00	6.19 ± 0.54		
Halothane-CO_2	8	p	16.6 ± 1.0	1.0 ± 0.04	6.2 ± 0.3(7)	0.75 ± 0.23	11.5 ± 1.02
	8	1	12.9 ± 1.1*	1.1 ± 0.05	7.09 ± 0.15(6)*	0.74 ± 0.27	9.0 ± 1.2
	8	7	16.5 ± 1.0	1.0 ± 0.03	6.45 ± 0.4(8)	0.75 ± 0.13	11.4 ± 0.9
Halothane-N_2O	8	p	16.6 ± 1.6(6)	1.0 ± 0.03		0.59 ± 0.23(8)	16.4 ± 2.3(8)
	8	1	14.4 ± 1.2(5)	1.0 ± 0.04		0.77 ± 0.24(7)	14.0 ± 2.8(7)
	8	7	16.0 ± 1.5(6)	1.0 ± 0.03		1.26 ± 0.71(5)	13.8 ± 2.2(6)
Fluroxene	11	p	14.7 ± 0.9	0.9 ± 0.00			
	11	1	13.2 ± 1.1	0.9 ± 0.00			
	11	7	16.8 ± 1.1	0.9 ± 0.00			
Diethyl Ether	10	p	15.5 ± 1.1(8)	0.9 ± 0.12(9)			
	10	1	10.0 ± 2.5(8)*	0.8 ± 0.13(9)			
	10	7	14.9 ± 2.8(7)	0.1 ± 0.9(8)			

Time: p = prior to anaesthesia, 1, 3 and 7 days after anaesthesia.
N = number of subjects. Variation of N in certain groups is indicated by ( ).
Normal values are: BUN 8–22 mg%, creatinine 0.5–1.2 mg%, uric acid 2–7 mg%. Lysozyme units are micrograms per ml. urine or plasma.
*Significantly different from control, $p < 0.05$.

TABLE IV

BLOOD ELECTROLYTES, PROTEINS AND GLUCOSE PRIOR TO, DURING AND FOLLOWING ANAESTHESIA. Mean values ± 1 standard error are shown

	N	Time	Sodium	Potassium	Chloride	Bicarbonate	Calcium	Phosphorus	Total Serum Protein	Albumin	Glucose
Isoflurane-O_2	7	p	139 ± 2	3.5 ± 0.1	102 ± 2	21.7 ± 0.6	9.4 ± 0.1	4.4 ± 0.2	7.3 ± 0.2	4.8 ± 0.1	77.0 ± 4.2
	7	1 hr.					9.0 ± 0.2	3.4 ± 0.3	6.7 ± 0.2*	4.3 ± 0.2	127.6 ± 9.2(5)*
	7	1	139 ± 2	3.5 ± 0.1	102 ± 1	22.3 ± 1.3	9.2 ± 0.1	3.4 ± 0.1*	6.8 ± 0.2*	4.5 ± 0.1*	109.3 ± 4.9*
	7	7	140 ± 2	4.0 ± 0.1*	101 ± 1	23.4 ± 0.9	9.9 ± 0.2*	3.9 ± 0.1	7.9 ± 0.2*	5.2 ± 0.1*	82.1 ± 1.8
Isoflurane-CO_2	10	p	140 ± 2	3.5 ± 0.1	102 ± 1	23.6 ± 1.0	9.7 ± 0.2	4.3 ± 0.2	7.5 ± 0.2	5.2 ± 0.1	81.7 ± 3.3
	10	1 hr.					9.1 ± 0.1	4.9 ± 0.4	6.8 ± 0.1*		127.6 ± 8.0(7)*
	10	1	139 ± 1	3.7 ± 0.1	101 ± 1	24.8 ± 0.9	9.5 ± 0.1	3.4 ± 0.1*	7.0 ± 0.1*	4.7 ± 0.1*	116.8 ± 9.7*
	10	7	139 ± 2	4.0 ± 0.1	103 ± 2	25.6 ± 0.7	10.0 ± 0.2	3.9 ± 0.2*	7.6 ± 0.2	5.2 ± 0.1	95.1 ± 4.2*
Isoflurane-N_2O	8	p	144 ± 1	3.6 ± 0.1	106 ± 1	25.0 ± 1.2	9.7 ± 0.1	4.6 ± 0.2	7.4 ± 0.1	5.0 ± 0.1	79.4 ± 2.1
	8	1 hr.	142 ± 2	4.5 ± 0.1*	108 ± 1	22.7 ± 0.4					129.0 ± 7.1(7)*
	8	1	141 ± 1	3.6 ± 0.1	106 ± 1	25.5 ± 0.4	9.1 ± 0.1*	3.5 ± 0.1*	6.8 ± 0.2*	4.4 ± 0.1*	103.1 ± 6.5*
	8	3					9.7 ± 0.1	4.3 ± 0.2	7.4 ± 0.2	4.8 ± 0.1	106.1 ± 12.3
	8	7	144 ± 2	4.6 ± 0.3*	106 ± 2	25.6 ± 0.8	9.8 ± 0.1	4.2 ± 0.2	7.6 ± 0.1	4.9 ± 0.2	87.6 ± 3.7*
Halothane-CO_2	8	p	141 ± 1	3.7 ± 0.1	105 ± 1.0	23.3 ± 0.7(7)	9.5 ± 0.1(7)	4.3 ± 0.2(7)	7.0 ± 0.1(7)	4.8 ± 0.1(7)	89.3 ± 6.3(7)
		1 hr.									110.9 ± 5.3(7)*
	8	1	138 ± 1	4.0 ± 0.2	104 ± 1.0	24.4 ± 0.8	8.9 ± 0.2(6)	3.5 ± 0.2(6)	6.4 ± 0.1(6)*	4.3 ± 0.1(6)*	119.0 ± 13.6(6)
	8	7	141 ± 1	4.3 ± 0.1*	105 ± 1.0	26.5 ± 0.8	9.7 ± 0.1(8)	3.9 ± 0.3(8)	7.4 ± 0.3(8)	5.0 ± 0.1(8)	76.4 ± 3.7(8)
Halothane-N_2O	8	p	142 ± 1	3.7 ± 0.1	104 ± 1	21.2 ± 0.8					92.1 ± 3.5
	8	1	139 ± 1	4.1 ± 0.1	103 ± 1	23.2 ± 1.0					118.0 ± 4.8
	7	7	141 ± 2	4.2 ± 0.1*	103 ± 1	22.7 ± 0.6					

Time: p = prior to anaesthesia, 1 hr = 1 hour after induction, 1, 3, and 7 = days following anaesthesia.
N = number of subjects, variation of N in certain groups is denoted by ( ).
Normal values: sodium 136–144 meq/L, potassium 3.5–5.3 meq/L, chloride 96–106 meq/L, bicarbonate 23–31 meq/L, calcium 9.2–10.5 meq/L, phosphorous 2.5–4.5 meq/L, total serum protein 6.5–8.4 gm%, albumin 3.5–5.2 gm% glucose 65–110 mq%.
*Significantly different from control, $p < 0.05$.

following exposure to isoflurane or halothane. These variables had returned toward control values by the seventh day after anaesthesia. Tests for occult blood, acetone, glucose, protein, bilirubin and microscopic examinations of the urine did not reveal significant abnormalities. No data from urinalyses were obtained for the fluroxene and diethyl ether groups.

Blood electrolytes, protein, glucose (Table IV)

Serum sodium and chloride values were unchanged throughout the period of observation for all anaesthetics. Potassium values increased significantly one hour after induction with isoflurane-nitrous oxide, the only group in which the measurement was made at that time. This may relate to the release of glucose (see below). Potassium values had increased on the seventh day after all anaesthetics. Bicarbonate content tended to increase on the first day after anaesthesia had increased further at seven days except in the group anaesthetized with halothane-nitrous oxide. Changes in both calcium and phosphorus values were small. Both decreased slightly at one day and had returned toward (phosphorus) or above (calcium) control values by seven days. Total serum protein and albumin values decreased significantly for all anaesthetics at one day. These changes probably reflect effects of blood removal (200–400 ml) and its replacement with electrolyte solution. All values returned to or above normal by seven days. One hour after induction, at a time when glucose had not yet been administered intravenously, blood glucose values had increased significantly with all isoflurane groups and with halothane-carbon dioxide. However, the increases were significantly greater in the isoflurane-carbon dioxide and isoflurane-nitrous oxide groups than in the halothane-carbon dioxide and halothane-nitrous oxide groups, respectively. The glucose was elevated one day after anaesthesia but this increase was clouded by the concomitant infusion of glucose.

Blood Elements (Table V)

Haematocrit values decreased in all groups at one day, probably again due to the 200 to 400 ml blood loss and replacement with electrolyte solution. By the seventh post-anaesthesia day the haematocrit values had returned toward control in all groups. Total leukocyte count increased in all groups at one day and had returned toward or below control values by the seventh day. Increases were greatest in the halothane-nitrous oxide and fluroxene groups on day one, due largely to increases in polymorphonuclear (PMN) leukocytes. Per cent increase of PMN was greater one day after halothane-carbon dioxide than after isoflurane but increases in absolute PMN were not different between these groups. There was no evidence of eosinophilia in any group.

Serum fluoride values showed a small increase at some period following isoflurane anaesthesia in three of four volunteers (Table VI). Values returned to control levels by day three in one volunteer and day seven in the other.

Discussion

The most striking conclusion from these studies is the relative innocuousness of halothane, fluroxene and diethyl ether as well as the new agent, isoflurane. Despite

TABLE V

HAEMATOCRITS, TOTAL LEUKOCYTE, AND POLYMORPHONUCLEAR CELL COUNTS PRIOR TO AND FOLLOWING ANAESTHESIA

	N	Time	Haematocrit %	Leukocytes per ml	Polymorphonuclear Leukocytes %
Isoflurane-O_2	7	p	43 ± 1	7329 ± 490	42.0 ± 4.0
	7	1	37 ± 1*	8460 ± 532	65.9 ± 2.5
	7	7	42 ± 0	6223 ± 333	51.1 ± 5.0
Isoflurane-CO_2	10	p	45 ± 1	6891 ± 469	54.1 ± 2.0
	10	1	41 ± 1*	8272 ± 531	69.0 ± 3.1
	10	7	42 ± 1*	6631 ± 372	58.1 ± 3.6
Isoflurane Nitrous Oxide	8	p	45 ± 1	8004 ± 454	48.1 ± 3.4
	8	1	40 ± 1*	9088 ± 967	67.6 ± 1.7
	8	7	41 ± 1*	6606 ± 617(6)*	51.7 ± 4.1(6)
Halothane-CO_2	8	p	43 ± 1	6440 ± 430	49.1 ± 3.0
	8	1	40 ± 1	8840 ± 900	73.6 ± 1.2(7)
	8	7	43 ± 1	5200 ± 480	53.0 ± 3.0
Halothane Nitrous Oxide	8	p	44 ± 1	6900 ± 500	50.0 ± 3.4
	8	1	41 ± 1(7)	9500 ± 500(7)*	80.5 ± 2.7
	8	7	42 ± 1	6100 ± 600	54.4 ± 2.6
Fluroxene	6	p	42 ± 1	5430 ± 450	59.5 ± 3.2
	6	1	40 ± 2	10820 ± 1580(5)*	81.0 ± 2.1(5)
	6	7	42 ± 1	5610 ± 750	56.0 ± 7.0(5)

TIME: p = prior to anaesthesia, 1 and 7 = 1 and 7 days following anaesthesia.
N = number of subjects, variation from N in certain groups is denoted by ( ).
*= Significantly different from control $p < 0.05$.

TABLE VI

SERUM FLUORIDE VALUES PRIOR TO AND FOLLOWING ISOFLURANE NITROUS OXIDE ANAESTHESIA IN FOUR VOLUNTEERS

Subject	Time	Serum Fluoride, micromoles/liter
1	Preanaesthesia	1
	Following 5 hours anaesthesia	1
	Postanaesthesia-1 day	1
2	Preanaesthesia	1
	Following 5 hours anaesthesia	4
3	Preanaesthesia	1
	Following 7 hours anaesthesia	3
	Postanaesthesia-1 day	2
	Postanaesthesia-3 days	1
4	Preanaesthesia	1
	Postanaesthesia-1 day	3
	Postanaesthesia-7 days	1

prolonged anaesthesia, sometimes at profound levels, despite occasional hypotension and despite supra-imposition of hypercapnia there was little evidence of significant impairment of hepato-renal function. The greatest deviation from normal had been reversed by day seven in all groups except the group exposed to halothane-carbon dioxide in whom the average BSP retention, though much lower than on day one, was still slightly above normal.

Although no serious deviations from normal hepatic function occurred either in individuals or in groups, the small differences between groups in BSP retention are noteworthy. Isoflurane anaesthesia was followed by the smallest increases in BSP retention. Several workers have suggested a possible causal relationship between

metabolism of anaesthetics and hepatic injury.[14-19] Halothane[14] and fluroxene[20,21] are both known to be metabolized whereas isoflurane metabolism is minimal or perhaps nonexistent.[22] Whether this explains the lower BSP retention following isoflurane remains unknown. Perhaps the explanation lies in the slightly smaller dose-time factor for the isoflurane groups (Table I). In any case, it appears that isoflurane is no more hepatotoxic in man than established agents.

Others have suggested that hypercapnia or hypotension enhance the abnormalities in hepatic function associated with halothane.[23] Our results do not support such a conclusion. Neither the isoflurane-carbon dioxide nor halothane-carbon dioxide groups differed from the isoflurane or halothane groups not subjected to hypercapnia. Further, the isoflurane-oxygen groups had lower arterial pressures than the isoflurane-nitrous oxide group, yet failed to show differences in hepatic effects.

The measures of renal function, with the possible exception of urine lysozymes, are not thought to be sensitive tests of renal injury. Would more sensitive tests have revealed differences between the agents studied? To this we have no answer. However, from review of other studies we believe that the tests we used would have demonstrated the nephrotoxicity of an agent such as methoxyflurane. Serum electrolytes, uric acid, and BUN all showed abnormalities in Mazze's[24] studies after methoxyflurane anaesthesia. Despite a greater dose-time stress, these values were normal in our subjects except for a small increase in uric acid one day after halothane-carbon dioxide.

It may be argued that our approach to the study of the hepatic or renal toxicity of anaesthetics has failed in that no hepatic or renal toxicity was revealed. This argument is especially pertinent in view of the accepted hepatotoxicity of halothane.[25] In part, we would answer that slight hepatotoxicity of halothane was demonstrated. In part the answer may lie in the mechanism by which halothane hepatotoxicity is produced. The rarity of this untoward event has suggested that certain individuals are peculiarly "sensitive" to halothane either by virtue of an allergic aberrancy[25] or a greater ability to metabolize halothane[26] and/or a decreased ability to withstand the noxious effects of its metabolites. The rarity of halothane hepatotoxicity suggests that more sensitive tests are unlikely to reveal this hepatotoxicity in a small group of healthy human volunteers. How to find the peculiarly sensitive individual either to protect him if he requires anaesthesia or to use him in a study of hepatotoxic effects is unclear. Such a person may be identified by a particular genotype; or the event may result from a prior drug exposure with consequent induction of enzymes which metabolize halothane.[26,27]

Perhaps the primary usefulness of this report relates to the search for a better anaesthetic.[28] Acceptance of such an agent requires that its renal or hepatic toxicity be no greater than that produced by currently available anaesthetics. The values presented in this report may be used as standards against which any new agent can be compared.

Summary

Comparisons of toxic effects of isoflurane, halothane, fluroxene and diethyl ether were made in human volunteers not undergoing surgical procedures. Comparisons

were made of effects on bromsulpthalein retention, serum glutamic oxaloacetic and pyruvic transaminases, lactic dehydrogenase, alkaline phosphatase, serum cholesterol, total serum protein and albumin, serum sodium, chloride, potassium, carbon dioxide content, uric acid, calcium, phosphorus, glucose, creatinine, fluoride, blood urea nitrogen, urine and plasma lysozymes, haematocrit, white blood cells, polymorphonuclear leukocytes and urinalysis.

We found greater increases in BSP after halothane and fluroxene than after isoflurane. Concomitant hypercapnia or hypotension did not influence the results. Serum glutamic oxaloacetic transaminase increased only after fluroxene. We found elevated polymorphonuclear leukocytes after all anaesthetics.

No serious toxicity occurred after any of the anaesthetics.

Résumé

Nous avons étudié, chez 60 humains volontaires, les effets de l'isoflurane ou de l'halothane avec ou sans protoxyde d'azote, du fluroxene et de l'éther diéthylique sur les fonctions hépatiques et rénales et sur les éléments du sang. La durée de l'anesthésie a varié de 5.3 à 7.3 heures. La profondeur de l'anesthésie a varié à l'intérieur de chaque étude et peut aller à des doses variant de 1.0 à 4.0 M.A.C. La rétention de Bromsulphtaleine (BSP) 45 minutes après l'injection d'une dose de 5 mg/kg a augmenté par rapport à la valeur pré-anesthésique de 2.9 pour cent à 5.8 pour cent après l'isoflurane; de 2.8 à 11.3 pour cent après l'halothane et l'hypercapnie qui l'accompagne; puis, de 2.5 à 7.7 pour cent après le fluroxène. Il n'est pas survenu de changements importants après l'isoflurane et l'hypercapnie qui l'accompagne, l'isoflurane et le protoxyde d'azote ou l'éther diéthylique. La ventilation spontanée et des tests de réponse au CO_2 conduisant à une hypercapnie (46 à 80 torr) au cours de l'anesthésie chez un groupe soumis à l'isoflurane et un groupe soumis à l'halothane n'ont pas produit de déviations plus grande du BSP que lorsque l'hypercapnie était absente. Malgré des pressions artérielles moyennes inférieures dans le groupe qui a reçu l'isoflurane seul (nadir 46 torr) à ceux du groupe qui a reçu isoflurane et protoxyde d'azote (nadir 73 torr) nous n'avons pas observé de plus grandes modifications du BSP dans le premier groupe. Les transaminases glutamiques oxaloacetiques sériques (S.G.O.T.) ont augmenté seulement après le fluroxène (18.4 unités avant l'anesthésie à 54.9 unités, une journée après l'anesthésie). Aucune modification rénale n'est apparue. Une augmentation des leucocytes polynucléaires est survenue après toutes les anesthésies. Nous n'avons pas dépisté de toxicité sérieuse avec le nouvel agent antsthésique, l'isoflurane, ni avec les autres produits.

Acknowledgments

Isoflurane (Forane, Trademark of Ohio Medical Products, Division of Air Reduction Company, Inc.) was supplied by Ohio Medical Products.

Halothane (Fluothane) was supplied by Ayerst Laboratories.

Fluroxene (Fluoromar) was supplied by Ohio Medical Products.

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