Brief Reports

Liver and renal function after repeated sevoflurane or isoflurane anaesthesia

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Purpose: To compare retrospectively liver and renal function after repeated exposure (twice) to sevoflurane or isoflurane.

Methods: Sixty patients were studied for liver and renal function after repeated exposure within 30 to 180 days to sevoflurane (30 patients) or isoflurane (30 patients). Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GTP), blood urea nitrogen (BUN) and creatinine (Cr) were measured before and, 1, 3, 7, and 14 days after surgery. Qualitative analyses of urinary protein and glucose were done 1, 3, and 7 days after surgery.

Results: The number of patients with abnormal values in AST, ALT and GTP was larger in the isoflurane than in the sevoflurane group. BUN and Cr were within normal range after anaesthesia in either group. Renal excretion of protein and glucose increased one and three days after anaesthesia with no difference between the anaesthetics. None of the variables showed differences between the first and second anaesthesia after either anaesthetic.

Conclusion: Repeat exposure to sevoflurane or isoflurane within 30 to 180 days had no additional risk of increasing serum concentration of liver enzymes or increasing urinary excretion of protein and glucose compared with the first exposure to the same anaesthetic.

Objectif : Comparer rétrospectivement la fonction hépatique et rénale après une exposition répétée (deux fois) au sévoflurane ou à l'isoflurane.

Méthodes : L'étude a porté sur la fonction hépatique et rénale de soixante patients évalués à la suite d'une exposition répétée, après 30 à 180 jours, au sévoflurane (30 patients) ou à l'isoflurane (30 patients). Les concentrations sériques d'aspartate aminotransférase (AST), d'alanine aminotransférase (ALT), de bilirubine totale (BilT), de phosphatase alcaline (PAL), de glutamyl-transpeptidase (GTP), d'azote uréique du sang (AUS) et de créatinine (Cr) ont été mesurées avant la chirurgie et, 1, 3, 7 et 14 jours après la chirurgie. Des analyses qualitatives de la protéinurie et de la glucosurie ont été faites, 1, 3 et 7 jours après la chirurgie.

Résultats : Le nombre de patients présentant des valeurs anormales de AST, de ALT et de GTP a été plus grand dans le groupe qui a reçu de l'isoflurane. L'AUS et la Cr sont demeurés dans les limites de la normale après l'anesthésie dans les deux groupes. La libération rénale de protéine et de glucose a augmenté, un et trois jours après l'anesthésie, sans différence entre les anesthésiques. Aucune différence de variable n'a été relevée entre la première et la seconde anesthésie, après l'emploi de l'un ou l'autre anesthésique.

Conclusion : L'exposition répétée au sévoflurane ou à l'isoflurane, après 30 à 180 jours, ne présente pas de risque additionnel d'augmentation des concentrations sériques des enzymes hépatiques ou de protéinurie et de glucosurie, par rapport à la première exposition au même anesthésique.

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BOTH sevoflurane and isoflurane are commonly thought to be less hepatotoxic than halothane and enflurane although, recently, liver dysfunction has been reported after sevoflurane[1] and after isoflurane[2] anaesthesia.

Repeated exposure to halothane led to a greater frequency of increased liver enzymatic activity than after repeated enflurane.[3] Only case reports are available concerning repeated sevoflurane or isoflurane anaesthesia. A 10 yr old child has been reported who showed no liver damage after five exposures to sevoflurane anaesthesia within 40 days.[4] Whereas, an obese woman developed fulminant hepatic failure 17 days after the third consecutive exposure to isoflurane.[5]

In this study, we retrospectively compared liver and renal function after repeat anaesthesia with sevoflurane and isoflurane.

Methods

After institutional review board approval, 60 patients (50 - 75 yr), who underwent elective neurosurgery or head and neck surgery under general anaesthesia twice within 30 to 180 days in two years, were retrospectively enrolled in this study. Patients who received sevoflurane (30 patients) or isoflurane (30 patients) anaesthesia were selected as the controls matched between groups. Patients who had had a history of general anaesthesia and alcohol or substance abuse, who have had hepatic, renal, circulatory, respiratory disease, and episodes of critical hypotension and bleeding on anaesthesia record, were excluded from the study.

Anaesthesia was induced with a) 0.1 $mg \cdot kg^{-1}$ midazolam and 3 $mg \cdot kg^{-1}$ thiopentone, b) 5 $mg \cdot kg^{-1}$ thiopentone or c) sevoflurane 5% inhalation with nitrous oxide 50% in oxygen and was maintained with sevoflurane or isoflurane and nitrous oxide (67%) in oxygen with a total flow of 6 $L \cdot min^{-1}$.

As routine, serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GTP), blood urea nitrogen (BUN) and creatinine (Cr) were measured before, and 1, 3, 7, and 14 days after surgery. Qualitative analyses of urinary protein and glucose were also performed. Those were judged as positive or negative. All variables were measured at the central laboratory in our hospital.

All data are expressed as mean ± standard deviation (SD). The minimum alveolar concentration (MAC) hours were calculated from the percent end-tidal anaesthetic concentration and the duration of exposure shown on the anaesthesia record. MAC values of 1.71% and 1.15% were used for sevoflurane and isoflurane, respectively. Abnormal values of the test were defined as a value which exceeded the upper limit of the normal range.

Demographic data were compared using the chi-square test, paired and non-paired t test and, when appropriate, the F test. The chi-square test was used to compare urinary analysis data between the two anaesthetics. Concentrations of AST, ALT, TBil, ALP, GTP, BUN, and Cr were analysed using two way repeated measures analysis of variance (ANOVA) followed by contrast. A $P < 0.05$ was considered statistically significant.

Results

There were no demographic differences between the groups (Table I).

The AST, ALT and GTP concentrations increased with peaks seven days after surgery (Table II). The number of patients with abnormal value in AST, ALT and GTP was larger in the isoflurane group than in the sevoflurane group (Figure). The BUN and Cr concentrations were within the normal ranges during the study in both anaesthesia groups. Transient positive proteinuria was observed in 5, 6, 5, and 7 patients of sevoflurane 1st, 2nd and isoflurane 1st, 2nd exposure, respectively. Glucosuria was seen in 1, 4, 1, and 3 patients of sevoflurane 1st, 2nd and isoflurane 1st, 2nd exposure, respectively. No variables showed differences between the first and second exposure in either anaesthetics.

Discussion

Liver function after inhalation anaesthesia depends on liver blood flow during anaesthesia, increased intracel-

TABLE I Demographic data

Group		*Sevoflurane*	*Isoflurane*
Male/Female		21 / 9	18 / 12
Age (yr)		61 ± 7	63 ± 8
Type of surgery			
Neurosurgery		17	16
Head and Neck surgery		13	14
Body weight (kg)		59.9 ± 6.9	61.7 ± 6.0
Interval between 1st. and 2nd. surgery (days)		65 ± 14	71 ± 20
Duration of anaesthesia			
(min)	1st	363 ± 85	335 ± 102
	2nd	324 ± 121	301 ± 110
Duration of surgery (min)			
	1st	285 ± 68	264 ± 94
	2nd	251 ± 82	233 ± 99
Blood transfusion			
Number of cases	1st	4 (425 ± 64)	4 (394 ± 72)
(volume)	2nd	6 (387 ± 85)	4 (391 ± 62)
Amount of inhalation	1st	4.9 ± 1.4	4.3 ± 1.2
anaesthetics (MAC·hr)	2nd.	4.2 ± 1.0	3.8 ± 1.1

mean ± SD, 1st: at the first surgery, 2nd: at the second surgery
MAC: minimum alveolar concentration, hr: hours

TABLE II Serum concentrations of liver enzymes and renal function test

Variables	*Group*		*Days after anaesthesia*				
			Pre	*1*	*3*	*7*	*14*
AST	Sev	1st	24 ± 9	21 ± 9	31 ± 8	39 ± 9*	25 ± 10
(9-37)		2nd	21 ± 9	25 ± 8	33 ± 9	37 ± 6*	22 ± 11
IU·L^{-1}	Iso	1st	27 ± 8	37 ± 9*†	48 ± 11*†	59 ± 16*†	37 ± 8*†
		2nd	24 ± 9	30 ± 10	41 ± 10*†	49 ± 13*†	41 ± 10*†
ALT	Sev	1st	23 ± 8	32 ± 9	36 ± 8*	51 ± 10*	37 ± 8*
(5-37)		2nd	25 ± 9	29 ± 8	31 ± 11	44 ± 12†	38 ± 7*
IU·L^{-1}	Iso	1st	24 ± 7	61 ± 15*†	72 ± 16*†	97 ± 25*†	71 ± 31*†
		2nd	27 ± 8	48 ± 10*†	58 ± 13*†	68 ± 26*†	51 ± 29*†
TBil	Sev	1st	0.6 ± 0.2	0.5 ± 0.2	0.5± 0.1	0.4 ± 0.2	0.4 ± 0.2
(0.3-1.0)		2nd	0.5 ± 0.2	0.4 ± 0.2	0.4± 0.2	0.4 ± 0.2	0.6 ± 0.2
mg·dL^{-1}	Iso	1st	0.5 ± 0.3	1.0 ± 0.4*†	0.6 ± 0.2	0.5 ± 0.3	0.4 ± 0.2
		2nd	0.4 ± 0.2	0.9 ± 0.3*†	0.6 ± 0.3	0.6 ± 0.2	0.5 ± 0.2
ALP	Sev	1st	94 ± 25	105 ± 18	113 ± 21	139 ± 25*	147 ± 36*
(37-147)		2nd	111 ± 12	109 ± 15	114 ± 13	125 ± 20	138 ± 29*
IU·L^{-1}	Iso	1st	110 ± 10	121 ± 20	134 ± 21	135 ± 33	128 ± 27
		2nd	109 ± 15	117 ± 14	132 ± 25	131 ± 21	119 ± 23
GTP	Sev	1st	32 ± 8	43 ± 10	55 ± 12*	71 ± 19*	62 ± 10*
(5-53)		2nd	41 ± 10	54 ± 11	55 ± 10	64 ± 12*	58 ± 9
IU·L^{-1}	Iso	1st	38 ± 6	49 ± 10	73 ± 17*†	124 ± 41*†	85 ± 28*†
		2nd	40 ± 9	55 ± 11	81 ± 19*†	103 ± 30*†	72 ± 18*†
BUN	Sev	1st	11 ± 3	12 ± 5	14 ± 3	15 ± 4	14 ± 3
(8-21)		2nd	13 ± 5	12 ± 4	11 ± 4	12 ± 6	13 ± 5
mg·dL^{-1}	Iso	1st	13 ± 3	12 ± 4	14 ± 4	12 ± 4	12 ± 5
		2nd	12 ± 4	13 ± 4	16 ± 7	15 ± 5	16 ± 4
Cr	Sev	1st	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.2	0.8 ± 0.1	0.8 ± 0.2
(0.6-1.1)		2nd	0.9 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	0.7 ± 0.2	0.6 ± 0.1
mg·dL^{-1}	Iso	1st	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
		2nd	0.8 ± 0.1	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.8 ± 0.1

mean ± SD, 1st: at the first anaesthesia, 2nd: at the second anaesthesia, *: $P < 0.05$ *vs* the control value (pre), †: $P < 0.05$ *vs* sevoflurane group. Normal range is indicated in the parenthesis. Pre: before surgery, Sev: sevoflurane group, Iso: isoflurane group, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBil: total bilirubin, ALP: alkaline phosphatase, GTP: γ-glutamyltranspeptidase, BUN: blood urea nitrogen, Cr: creatinine

lular calcium concentration ([Ca^{++}]i), metabolites of anaesthetics, and other drugs used perioperatively. Liver blood flow does not differ between sevoflurane and isoflurane anaesthesia.[6] There are no reports of [Ca^{++}]i in sevoflurane anaesthesia, while [Ca^{++}]i was found to be lower in isoflurane anaesthesia than in halothane or enflurane anaesthesia.[7] Other drugs were not taken into consideration in the present study because they could not be controlled.

Halothane, enflurane, isoflurane, and desflurane but not sevoflurane produce trifluoroacetyl acid (TFA), which as a hapten induces hypersensitivity.[8] This might increase liver injury after second exposure to TFA, i.e. exposure to halothane,[9] enflurane or isoflurane. Multiple administration of sevoflurane in monkeys induced transient increase of serum concentration of liver enzymes in a week, but no gross pathological, histopathological, or ultrastructural differences were found.[10] The interval of 30 to 180 days was chosen in the present study because of the limited number of patients in our institution. The present study showed no differences of postoperative liver function detected

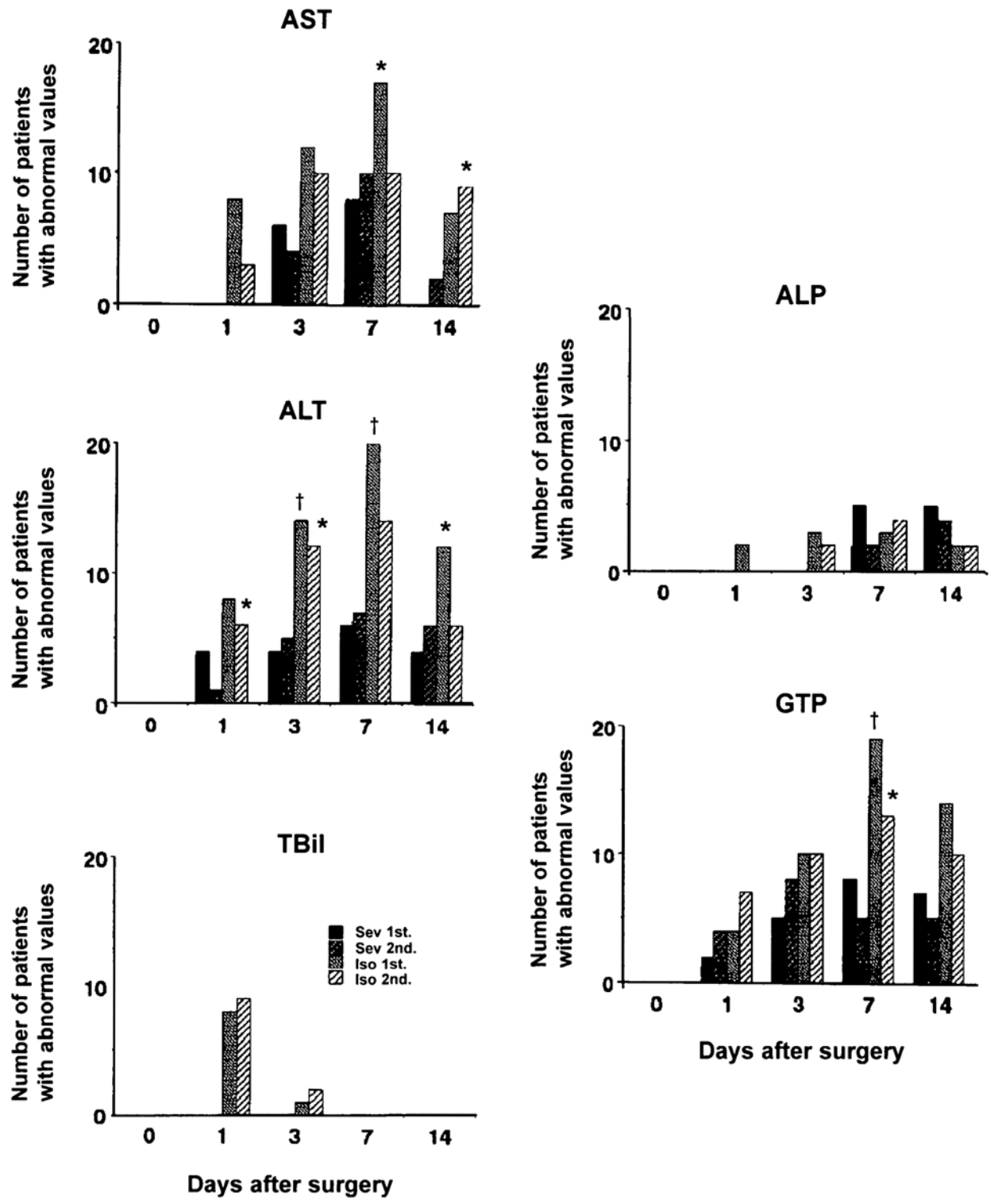

FIGURE The number of patients who had abnormally high serum concentrations of liver enzymes
AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBil: total bilirubin, ALP: alkaline phosphatase, GTP: γ-glutamyl transpeptidase, Sev: sevoflurane group, Iso: isoflurane group, 1st.: at the first surgery, 2nd.: at the second surgery, Total number of patients tested in each group was 30. *: $P < 0.05$ *vs* sevoflurane group, †: $P < 0.01$ *vs* sevoflurane group, No abnormal values were observed in blood urea nitrogen (BUN) and creatinine (Cr). There were no significant differences between the first and second time in both anaesthetics.

by routine clinical examination between the first and second sevoflurane or isoflurane exposure with the interval of 30 to 180 days. Further study is necessary to verify the result of animal study[10] in human.

The present study showed no clinical renal injury except for transient proteinuria and glycosuria. Proteinuria indicates glomerular injury and increased urinary glucose suggests proximal tubular injury. This transient abnormal excretion of protein and glucose may not be unique for one anaesthetic, because no difference was observed between sevoflurane and isoflurane anaesthesia in the severity of proteinuria and glycosuria.

There are no previous reports of renal function after repeated sevoflurane or isoflurane anaesthesia. No exacerbation in renal function is suggested by the present study following second exposure to sevoflurane or isoflurane. The number of patients was too small to detect possible differences between two anaesthetics.

In conclusion, second exposure to sevoflurane or isoflurane within 30 to 180 days produced no additional risk of increased serum concentrations of liver enzymes or increased urinary excretion of protein and glucose compared with the first exposure to the same anaesthetic.

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